[redacted] **COUNTY COURT OF COMMON PLEAS**
CLEVELAND, OHIO

STATE OF OHIO

v.

[redacted]

Defendant

CASE NO. [redacted]

Judge [redacted]

- **MOTION TO COMPEL CCDCFS RECORDS**
- **BRIEF IN SUPPORT OF MOTION & IN OPPOSITION TO COURT ORDER**

Defendant has requested the entire record file previously provided to the court by the [redacted] County Department Children and Family Services ("[redacted]") regarding the alleged child victim in this matter. Prior Defense Counsel made a partial request of the file which was apparently not objected to by the State. After in-camera review of the records, current Defense Counsel has made a request for all the records.

Defendant's position is that the records – which document a long history of violent physical abuse in the alleged victim's home - are 1) fundamental to understanding the accuser's frame of mind/motivation for what the Defendant asserts are wildly false accusations, 2) necessary to assist Defendant's yet-to-be-retained forensic psychologist in preparing an expert report, which will 3) be vital in Defense Counsel's preparation for his cross-examination of the alleged victim. The prosecutor, "after discussing Defense Counsel's position with her supervisor [Sex Crimes division of the prosecutor's office]", remarked that "we have never heard of this strategy" and objected to the Defendant's request.

The prosecutor has not raised the rape shield statute in her opposition, nor any aspect of Section 10A of the Ohio Constitution, but simply argues only that she and her supervisor don't understand Defense Counsel's inchoate formulation of potential lines of questioning of the victim,

questions that will be designed to be probative of the victim's capacity for veracity, to expose the victim's credibility for the jury, and to establish the victim's competency to testify, the latter issue to be raised by separate motion of the Defendant.

Although a much more efficient and rule-based approach would be for the State to simply object to questions which are based on the alleged victim's past incidents of abuse, whether asked during cross exam or answered during expert direct testimony, as being irrelevant or prejudicial or beyond the scope, the court has ordered Defense Counsel to support his inchoate strategy with a brief. However, relevancy in this instance is either an Ohio Evidence Rule 404(B) and/or Rule 608(B) analysis, as set forth *infra*, and is dispositive of the State's objection without necessitating that the court step in and impede defense strategy prematurely and without any legal basis.

Thus, to the extent that a relevancy/prejudicial analysis for discovery purposes is to be utilized by this court to judge the merit of an inchoate defense strategy, the Defendant states that the insertion by the court at the State's urging into Defendant's strategy is unconstitutional and potentially rises to the level of both judicial and prosecutorial misconduct. Defense Counsel/Defendant thus object to the court's order to brief the basis for defense strategy.

However, Defense Counsel will comply with the court's request and provide a summary of the basis of his position.

I. DEFENDANT OBJECTIONS IN OPPOSITION TO COURT REQUEST

A. INTERFERENCE WITH TACTICS & DENYING DEFENDANT EXCULPATORY/IMPEACHMENT EVIDENCE IS MISCONDUCT

The Ohio Supreme Court has held: "Every trial court has a responsibility to conduct a trial in an orderly fashion and to ensure that a defendant receives a fair trial. *See* *State v. Fears,* 86 Ohio St.3d 329, 353, 1999 Ohio 111, 715 N.E.2d 136 (1999) (Moyer, C.J., dissenting). However, "trial

courts cannot interfere with counsel's trial tactics or representation of their clients." *State v. Hill*, 75 Ohio St.3d 195, 212, 1996 Ohio 222, 661 N.E.2d 1068 (1996)." *State v. Jackson*, Supreme Court of Ohio, 141 Ohio St. 3d 171 (2014).

The test for prosecutorial misconduct is whether the conduct complained of deprived the defendant of a fair trial. *State v. Apanovitch* (1987), 33 Ohio St. 3d 19, 24, 514 N.E.2d 394, 400; *State v. Fears*, 86 Ohio St. 3d 329 (1999).

In chambers this past week, in arguing against producing the entire CFS file, the prosecutor stated - in response to Defense Counsel's assertion that the alleged victim lied on the police report about the Defendant driving past her school - that "[the victim] never said that." The alleged victim certainly did say that - in her very first report of this crime to [redacted] Police Department Incident Report, relevant excerpt attached as Exhibit A.) In fact, in her statement the alleged victim said, "that a male had been following her." The prosecutor falsely indicated in chambers during discussion that the victim did not place the "follower" at her school; the truth is that the victim stated that "the male was messaging her [and] riding pass (sic) her school and that he was watching her." (Exhibit A.) Phone records will show both these allegations to be lies: the Defendant never messaged the alleged victim, and the location services data from his cell phone carrier will show that the Defendant was never in the vicinity of the alleged victim's school.

Further, and even more egregious, the follow-up statement by the alleged victim is replete with even more lies. She states that the Defendant messaged her via "fake Instagram accounts." The State has provided 17,000+ pages of Instagram records in discovery, and the Defendant's name doesn't appear once. Neither does the State's Indictment or Bill of Particulars indicate any such activity by the Defendant or describe an email or URL controlled by the Defendant. The

alleged victim also states that she had sex with the Defendant (apparently voluntarily because there is no allegation of force) in the back of a "[redacted]." The Defendant was not in possession of a [redacted] at any time relevant herein. Finally, the alleged victim has changed and/or provided vague dates of the alleged sexual activity and in fact there are no specific dates associated with any of the accusations in the charges against Defendant.

The alleged victim will easily be established as a liar through the State's own evidence. Prudent lawyering mandates that the reasons for the lies, including any underlying mental health issues precipitated or exacerbated by the incidents of abuse that occurred throughout the alleged victim's entire life, be explored. Defendant's expert witness will need to know the alleged victim's entire CFS history, and more, to conduct a proper evaluation of the alleged victim's mental health.

The **Seventh Appellate District of Ohio** has stated in *State v. Telego*, Court of Appeals of Ohio, Seventh Appellate District, 2018-Ohio-254 (Mahoning County 2018):

> A claim of prosecutorial misconduct is not reversible unless the prosecutor's challenged act injected the trial with unfairness so as to constitute a denial of due process. State v. McKelton, 148 Ohio St. 3d 261, 2016-Ohio-5735, ¶ 257, 70 N.E.3d 508. A two-pronged test is applied asking: (1) whether the conduct was improper, and (2) whether it prejudicially affected the defendant's substantial rights considering the context of the entire trial. Id. The key concern is "the fairness of the trial, not the culpability of the prosecutor." State v. Hanna, 95 Ohio St. 3d 285, 2002-Ohio-2221, 767 N.E.2d 678, ¶ 61, quoting Smith v. Phillips, 455 U.S. 209, 219, 102 S.Ct. 940, 71 L.Ed.2d 78 (1982).
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> [*P23] "The limitation of * * * cross-examination lies within the sound discretion of the trial court, viewed in relation to the particular facts of the case." State v. Acre, 6 Ohio St.3d 140, 145, 6 Ohio B. 197, 451 N.E.2d 802 (1983). "***Cross-examination shall be permitted on all relevant matters and matters affecting credibility***." [emphasis added]. Evid.R. 611(B). "A questioner must have a reasonable basis for asking any question pertaining to impeachment that implies the existence of an impeaching fact." Evid.R. 607(B).
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> [*P24] On allegations of prosecutorial misconduct during questioning of the defendant, it has been concluded, "a cross-examiner may ask a question if the examiner has a good-faith belief that a factual predicate for the question exists." State v. Gillard, 40 Ohio St.3d 226, 230-231, 533 N.E.2d 272, 277, 535 N.E.2d 315 (1988) (finding it was not prosecutorial misconduct "to ask [the defendant] questions without presenting evidence of

> the allegations implied therein after [the defendant] had denied them").1 The Court pointed out how "effective cross-examination often requires a tentative and probing approach to the witness' direct testimony, and this cannot always be done with hard proof in hand of every assumed fact." Gillard, 40 Ohio St.3d at 231, quoting Hazel v. United States, 319 A.2d 136, 139 (D.C.App.1974).

In formulating his tactic - to expose and explain to a jury why a child abuse victim might struggle with the truth or fabricate allegations - via the paradigm of *CFS records ~ ACE score ~ maladaptive personality manifestation* (see *infra*), Defense Counsel is staying well within "effective cross-examination" and is doing nothing less or more than diligently building his "good-faith belief that a factual predicate for the [line of] question exists."

In fact, the **Fifth Appellate Court of Ohio** has held in *State v. Daugherty*, Court of Appeals of Ohio, Fifth Appellate District, 41 Ohio App. 3d 91 (Stark County 1987), quoted below by the **Second Appellate Court of Ohio** in *State v. Evans* (cite below) that a mistrial is risked if a good-faith implied assertion of truth in a question is not subsequently supported by information ***which is not otherwise in evidence***:

> A witness may be asked a question on cross examination "if the examiner has a good-faith belief that a factual predicate for the question exists." ***State v. Gillard*** (1988), 40 Ohio St. 3d 226, 533 N.E.2d 272, paragraph two of the syllabus. The contrary, of course, makes it improper for an examiner to ask a question in bad faith, in other words, a question which puts information before a jury that is not supported by the evidence. ***State v. Smidi*** (1993), 88 Ohio App. 3d 177, 183, 623 N.E.2d 655. In fact: it is grounds for a mistrial when a lawyer in a jury case rests his case, having failed to adduce any admissible evidence of information harmful to his adversary that he has, in the presence of the jury, asserted to be true in a question and that was denied by an adverse witness where the information is not otherwise in evidence.
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> **[*8]** This particularly applies to prosecutors in light of a defendant's right to a fair trial. ***Id.*** In *Daugherty*, the prosecutor posed a question to the defendant stating that employment records would reveal the defendant and her witness left work much earlier than they had both testified. ***Id.*** at 91. Thereafter, the prosecutor did not present proof of these records, nor any employer who could verify the statement. ***Id.*** at 92. After the defendant was convicted, the trial court *sua sponte* subpoenaed the employment records to find out that in fact the defendant and her witness had told the truth. During this hearing, the trial court stated that it was sufficiently convinced the prosecutor really had spoken to the girls' employer. The fact that the trial court believed this lends credence to the expectation that

> the jury also believed it, thereby placing great emphasis on the "testimony" of the prosecutor. The *Daugherty* appellate court found this to be sufficiently damaging to warrant a mistrial, and granted same. *Id. State v. Evans*, Court of Appeals of Ohio, Second Appellate District, 2001-Ohio-1523 (Montgomery County 2001).

Defense Counsel is attempting to build support for his informational belief that the alleged child victim in this case has severe interpersonal defects as the result of trauma prior to these allegations, trauma which interferes with her thought processes, logic, even reality. Contrary to the prosecutor's attempt to put a bad-faith motive on Defense Counsel's actions, Defense Counsel is operating from nothing but a good-faith perspective that the abuse documented in the CFS records is foundational to establishing a viable defense theory. Defense Counsel is not attempting to prove that the alleged victim is a liar per se – and so told the prosecutor in chambers that calling a child a liar by nature is not his style - but is the victim of child abuse, prior to these allegations, which form the basis for a logical and scientific explanation of her false allegations in this matter.

Finally, and most importantly - and assuredly beyond the prosecutor's anticipated scope - the CFS records will fulfill the "otherwise in evidence" standard necessary to avoid a mistrial if the victim simply denies suffering from trauma induced disorders during cross-examination.

Limiting the Defendant's strategy from the outset serves no legal, equitable, or judicial purpose. The reality is that the State's attempt to limit Defendant's, and thus the jury's, ability to understand and expose the alleged victim's motivations, including trauma and its effects, is a thinly veiled attempt to limit exculpatory and/or impeachment evidence.

The State is simply impeding Defense Counsel's efforts, undoubtedly because the prosecutor fears the results.

This court should not be a party to such nefarious actions by the prosecutor.

B. IMPROPER LIMITATION OF DEFENSE TACTICS INCLUDING CROSS-EXAMINATION IS UNCONSTITUTIONAL & VIOLATIVE OF OHIO EVIDENCE RULE 404(B)

The United States District Court, Northern District of Ohio Eastern Division has published a Magistrate habeas corpus opinion which succinctly summarizes Ohio state law on the issue that unless counsel raises a constitutional error upon a trial court's exclusionary evidentiary ruling, the constitutional error cannot be raised on appeal. *State v. Solether*, No. WD-07-053, 2008 WL 4278210 (Ohio Ct. App. Sept. 19, 2008). The opinion states, "Solether now argues that "it is abundantly clear that Solether's entire argument at the state court level focused on his trial counsel's inability to meaningfully cross-examine and confront the state's witness due to the trial court's erroneous exclusion of a key exhibit from evidence. . . [which] is the crux of the Sixth Amendment Confrontation Clause." (Doc. 9, at 3.) However, Solether did not raise the Confrontation Clause in his third assignment of error on appeal, neither explicitly nor implicitly. Instead, Solether argued this claim as a violation of the rules of evidence, and did not rely on federal cases, or "state cases employing federal constitutional analysis." See generally doc. 8, RX 11, at 21-23. The state court of appeals therefore did not rule on any federal issue but found that the trial court had not abused its discretion and found the assignment of error not well-taken. (Doc. 8, RX 18, at 16; Solether, 2008 WL 4278210, at *6-*7.) Moreover, the Supreme Court of Ohio will not consider a constitutional question which was not raised and argued in the lower courts. Leroy v. Marshall, 757 F.2d 94, 99 (6th Cir.), cert. denied, 474 U.S. 831 (1985); State v. Phillips, 27 Ohio St.2d 294, 302, 272 N.E.2d 347, 352 (1971).

A defendant always has the constitutional right to present a complete defense. Nonetheless, the court has the discretion to keep the proceedings within manageable limits and to curtail exploration of collateral matters. However, if the counsel has a good faith

basis for eliciting evidence, extrinsic proof tending to establish a reason to fabricate is never collateral and may not be excluded on that ground.

The Ohio Supreme Court, *State v. Graham*, 164 Ohio St. 3d 187 (2020) held that the standard for admitting extrinsic evidence introduced under Ohio Evidence Rule 404(B) is "the Williams test: We must determine whether this evidence was relevant. The question is not whether the evidence was relevant to the ultimate question of guilt but whether the evidence was relevant to the particular purpose for which it was offered. Hartman, 161 Ohio St. 3d 214, 2020-Ohio-4440, 161 N.E.3d 651, at ¶ 26. [T]he other-acts evidence must be probative of a 'purpose other than the person's character or propensity to behave in a certain way.' The Court went on:

> [**P71] Evid.R. 404(A) is a general prohibition on using evidence of a person's character to prove that he acted "in conformity therewith on a particular occasion." Evid.R. 404(B) provides:
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> **[*202]** Evidence of other crimes, wrongs or acts is not admissible to prove the character of a person in order to show action in conformity therewith. It may, however, be admissible for other purposes, such as proof of motive, opportunity, intent, preparation, plan, knowledge, identity, or absence of mistake or accident.
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> [**P72] In *State v. Williams*, 134 Ohio St.3d 521, 2012-Ohio-5695, 983 N.E.2d 1278, ¶ 20, we set forth a three-part analysis for determining the admissibility of other-acts evidence: to be admissible, (1) the evidence must be relevant, Evid.R. 401, (2) the evidence cannot be presented to prove a person's character to show conduct in conformity therewith but must instead be presented for a legitimate other purpose, Evid.R. 404(B), and (3) the probative value of the evidence cannot be substantially outweighed by the danger of unfair prejudice, Evid.R. 403. The admissibility of other-acts evidence pursuant to Evid.R. 404(B) is a question of law. *State v. Hartman*, 161 Ohio St. 3d 214, 2020-Ohio-4440, 161 N.E.3d 651, ¶ 22. The court is precluded from admitting improper character evidence under Evid.R. 404(B), but it has discretion to allow other-acts evidence that is admissible for a permissible purpose. *Hartman* at ¶ 22, citing *Williams* at ¶ 17.

Defense Counsel does not intend to use the documentation of abuse in the CFS records as "other acts" to show that the alleged victim has a propensity to lie now because she perhaps lied about any of the CFS events. Nor will the records be used to show that the alleged victim acted in

conformity with such a propensity - if it exists - in accusing the Defendant. (Defense Counsel has sufficient evidence from the State that the alleged victim has lied.) Neither will Defense Counsel use the CFS records to try and prove that the Defendant is not guilty because the victim suffered prior abuse. The "particular purpose" for which the CFS records are sought is to assist Defense Counsel and his expert in establishing that the alleged victim is high-risk for maladaptive personality disorder(s) which cause, perhaps in this case, illogical and phantom thought and action. Such proof, if the jury finds it credible and justified, will naturally assist in undermining the alleged victim's credibility, without Defense Counsel ever calling the alleged victim a liar. Defense Counsel and his expert should be permitted to pursue any proof that would make the alleged victim appear less credible, less logical, perhaps not competent, and suffering from maladaptive personality traits, all permitted purposes under 404(B)'s "other purposes, such as proof of motive, opportunity, intent, preparation, plan . . ."

Additionally, Defendant's expert will testify that one of the traits associated with the type of personality disorder commonly resulting from childhood trauma – Borderline Personality Disorder ("BPD") – is a tendency in "relationships" to fabricate not only perceived affection and rejection, but also to act out in revenge to a great degree. Defendant will testify that he had a passing acquaintance with the alleged victim, and that she was the one that engaged him in conversation which was flirtatious and inappropriate. Defendant's expert will also testify that someone suffering from BPD often misperceives another's behavior and reacts in illogical ways, including making false accusations. Under this analysis, proof of the alleged victim's intent to lie, intent which will be shown to be precisely embedded in and emanating from her mental health issues, is permitted to be established by extrinsic evidence.

The Ohio Supreme Court has held: "When a defendant challenges a trial court's limitation on cross-examination on appeal, the standard of review turns on the nature of the limitation. Limitations * * * that deny a defendant the opportunity to establish that the witnesses may have had a motive to lie infringe on core Sixth Amendment rights and are reviewed de novo." State v. Gonzales, 151 Ohio App.3d 160, 2002-Ohio-4937, ¶ 45, 783 N.E.2d 903 (1st Dist.), quoting United States v. Nelson, 39 F.3d 705, 708 (7th Cir.1994). To establish a confrontation violation, then, McKelton must show that he was "prohibited from engaging in otherwise appropriate cross-examination." Van Arsdall at 680. But if a trial court "allow[ed] cross-examination to expose a motive to lie," then "it is of peripheral concern to the Sixth Amendment how much opportunity defense counsel gets to hammer that point home to the jury." Nelson at 708. Under those circumstances, the extent of cross-examination is within the sound discretion of the trial court. State v. Freeman, 7th Dist. Jefferson No. 07JE5, 2008-Ohio-2925, ¶ 12, citing State v. Green, 66 Ohio St.3d 141, 147, 1993 Ohio 26, 609 N.E.2d 1253 (1993). To prove a violation of Evid.R. 611, McKelton must [*292] demonstrate that the trial court's limitation on cross-examination was "unreasonable, arbitrary or unconscionable." *State v. McKelton*, Ohio Supreme Court, 148 Ohio St. 3d 261 (2016).

This is a he-said/she-said case. Nothing is more relevant than credibility.

II. ADVERSE CHILDHOOD EVENTS & EFFECTS ARE PERMISSIBLE EVIDENCE UNDER OHIO EVIDENCE RULE 616(B)

The CFS records are extrinsic proof that the alleged victim in this matter has been abused, witnessed abuse, and was involved in a household rife with legal misconduct over an extended period of time. Defense Counsel holds the good-faith opinion that being exposed to such Adverse Child Experiences, referred to by mental health experts as "ACEs" (see U.S. Department of Health

& Human Services, "Adverse Childhood Experiences", https://www.childwelfare.gov/topics/preventing/overview/framework/aces/; see also attached Exhibits B and C, incorporated herein), can grossly affect a child's ability to perceive and participate in interpersonal relationships. According to The National Child Traumatic Stress Network organization:

> Certain types of childhood adversity are especially likely to cause trauma reactions in children. A child with a complex trauma history may be easily triggered or "set off" and is more likely to react very intensely. The child may struggle with self-regulation (i.e., knowing how to calm down) and may lack impulse control or the ability to think through consequences before acting. As a result, complexly traumatized children may behave in ways that appear unpredictable, oppositional, volatile, and extreme. A child who feels powerless or who grew up fearing an abusive authority figure may react defensively and aggressively in response to perceived blame or attack, or alternately, may at times be overcontrolled, rigid, and unusually compliant with adults. If a child dissociates often, this will also affect behavior. Such a child may seem "spacey", detached, distant, or out of touch with reality. Complexly traumatized children are more likely to engage in high-risk behaviors, such as self-harm, unsafe sexual practices, and excessive risk-taking such as operating a vehicle at high speeds. They may also engage in illegal activities, such as alcohol and substance use, assaulting others, stealing, running away, and/or prostitution, thereby making it more likely that they will enter the juvenile justice system. https://www.nctsn.org/what-is-child-trauma/about-child-trauma.

ACE research suggests that maladaptive personality disorders manifest in a high number of abuse victims, the most prevalent disorder being Borderline Personality Disorder. According to the *American Journal of Psychiatry,* "patients with borderline personality disorder are particularly likely to evoke boundary violations, including sexual acting out. These patients apparently constitute the majority of patients who falsely accuse therapists of sexual involvement." Volume 146, Issue 5 (May 1989, pps. 597-602; published online: 1 Apr 2006 https://doi.org/10.1176/ajp.146.5.597). See also "Pathways to False Allegations of Sexual Harassment", *Journal of Investigative Psychology and Offender Profiling,* William O'Donohue, University of Nevada, Reno, January 2006), abstracted:

> This paper gives an overview of the intricacies associated with sexual harassment investigations and enumerates 14 possible pathways to false allegations: lying; borderline personality disorder, histrionic personality disorder, psychosis, gender prejudice, substance abuse, dementia, false memories, false interpretations, biased interviews, sociopathy, personality disorders not otherwise specified, investigative mistakes, and mistakes in determination of the degree of harassment.

The Defendant will testify that in his limited interaction with the alleged victim that she was unable to maintain proper boundaries, in being overly flirtatious and solicitous, and in making inappropriate comments about the nature of [redacted] and in fact "cyber-stalked" the Defendant to discover [redacted] engaging the Defendant in conversation about this activity.

Whether or not the mental health of a witness is relevant turns on a good-faith foundation for the inquiry. **Tenth Ohio Appellate District**: "Defense counsel inquired into Barragan's mental health, and asked Barragan if he had been hospitalized as a result of his mental health. Barragan responded, "no." (Tr. Vol. I, at 194.) Appellee objected and inquired into a good-faith basis for the question concerning Barragan's alleged hospitalization. Defense counsel was unable to provide other than double hearsay as a foundation for questions of Barragan's hospitalization. Therefore, we determine that without defense counsel articulating a good-faith basis for questioning Barragan about his mental health, the trial court did not abuse its discretion in limiting defense counsel's cross-examination concerning Barragan's mental health. See *State v. Dennis* (Nov. 22, 1995), Marion App. No. 9-95-9, 1995 Ohio App. LEXIS 5234(without a good-faith basis, defense counsel's inquiry of the witness' psychiatric condition was irrelevant and, was therefore, properly excluded by the trial court). *State v. Ramirez*, Court of Appeals of Ohio, Tenth Appellate District, 2002-Ohio-4298 (Franklin County, 2002).

Establishing the alleged victim's ACE "score" – essentially the number and nature of abusive and neglectful events - through her CFS records, and other relevant records to be

determined, is essential for the Defendant's ability to show that the alleged victim is simply not credible and perhaps not competent.

The **Eleventh Ohio Appellate District** has stated**:** "The court in State v. Lowe, 164 Ohio App.3d 726, 2005 Ohio 6614, at P10-11, 843 N.E.2d 1243, stated: [*P114] "By its nature, cross-examination often involves a tentative and probing approach to testimony given on direct examination. State v. Gillard (1988), 40 Ohio St.3d 226, 231, 533 N.E.2d 272, 535 N.E.2d 315 ***. Therefore, the examiner need not lay an evidentiary foundation before posing questions upon cross-examination. It is sufficient if there is a good-faith basis to question the witness on the subject. Id." *State v. Henry*, Court of Appeals of Ohio, Eleventh Appellate District, 2009-Ohio-1138 (Lake County 2009).

The **Second Ohio Appellate District** has ruled on the interplay of good-faith and Ohio Evidence Rule 616(B):

> "Deaton also argues in support of his assignment of error that he should have been permitted to inquire concerning the ability of the complaining witness to perceive and remember events accurately. Specifically, he was not allowed to inquire whether Turner was using prescription drugs within the 48 hours preceding her testifying at the trial, or whether she was using medication at the time of the altercation with Deaton "that might affect your memory or perception of things going on." He was allowed to inquire whether there was anything that would alter Turner's perception of what was taking place in the courtroom during her testimony, to which Turner responded in the negative.
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> [*P18] The trial court did not provide any explanation for its rulings.
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> [*P19] The State acknowledges that Evid. R. 616(B) permits evidence of a defect of capacity, ability, or opportunity to observe, remember, or relate, to be shown to impeach a witness. But the State argues that this ability to impeach is limited by Evid. R. 607(B), which provides as follows: "A questioner must have a reasonable basis for asking any question pertaining to impeachment that implies the existence of an impeaching fact." The State argues that because Deaton had no reasonable basis to believe that Turner was impaired, either at the time of the altercation, or at the time of her testimony at trial, the trial court properly sustained the State's objection.

[*P20] Evid. R. 607(B) does not require a reasonable basis for any question pertaining to impeachment. It requires a reasonable basis for questions pertaining to impeachment "that impl[y] the existence of an impeaching fact." The staff notes to Evid. R. 607(B) contain the following explanation of this requirement:

Note that the requirement of a good faith basis applies only when the cross-examiner is effectively asserting in the form of a question the truth of a factual statement included within the question. If the cross-examiner is merely inquiring whether something is or is not true, a good faith basis is not required. Thus the question, "Your glasses were being repaired at the time of the accident, weren't they?" requires a good faith basis, while the question, "Were you wearing your glasses at the time of the accident?" does not.1 Graham, Handbook of Federal Evidence § 607.2, at 679-80 (4th ed. 1996).

[*P21] The questions Deaton put to Turner are of the permitted kind. Deaton asked Turner whether she had taken any prescription drugs within the 48 hours preceding her testimony. This question does not imply that Turner was taking prescription drugs. Similarly, Deaton asked Turner whether she was taking any medication at the time of the altercation that might have affected her memory or perception. This question, also, does not imply that Turner was taking any medication at the time; it merely asks if she was.

[*P22] Deaton had no way to take Turner's deposition before trial, or otherwise to determine whether Turner was taking prescription drugs at either time. Deaton could have attempted to interview Turner before trial, but given the history of hostility between them, it is not likely that Turner would have agreed to do so. Realistically, the only way for Deaton to find out if Turner was on medications that might have affected her perception or memory was to ask Turner, under oath. These questions were permitted under Evid. R. 616(B), and were not prohibited under Evid. R. 607(B), because they were not questions that implied the existence of an impeaching fact.

[*P23] The State cites State v. Edwards, 8th Dist. Cuyahoga No. 87587, 2006 Ohio 5726. The opinion in that case does not state what the question was, but it does state that the question implied the existence of an impeaching fact, which would be prohibited by Evid. R. 607(B).

[*P24] The State next cites State v. Totarella, 11th Dist. Lake No. 2002-L-147, 2004 Ohio 1175. In that case, the defendant was permitted to establish that the witness was under psychiatric care and was taking medication. The defendant was also permitted to ask the witness whether these medications affected the ability of the witness to perceive the events concerning which she testified. The trial court sustained an objection to inquiry into the specific condition for which the witness was taking the medication, after the trial court had satisfied itself that the condition was not relevant to the ability of the witness to perceive and to relate events. Id., ¶ 40-41. Totarella is readily distinguishable from the case before us, in which Deaton was not allowed to ask the witness whether she was taking any prescription drugs that might have affected her perception or memory.

> [*P25] In State v. Dennis, 3rd Dist. Marion No. 9-95-9, 1995 Ohio App. LEXIS 5234 (Nov. 22, 1995), another case cited by the State, the court of appeals upheld the trial court's having sustained an objection to an inquiry into whether the complaining witness had been taking any prescribed drugs on the night of the incident, finding that there was no good-faith basis for the question because urinalysis of the complaining witness disclosed the use of alcohol and marijuana or hashish, but not prescription drugs or medications. Since the use of prescription drugs had been ruled out by forensic evidence, we conclude that Dennis is distinguishable, but to the extent that it is not distinguishable, we do not find it persuasive.
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> [*P26] Finally, the State cites State v. Ramirez, 10th Dist. Franklin No. 01AP-859, 2002 Ohio 4298. In that case, the court of appeals found that the trial court had not erred in sustaining an objection to an inquiry whether a witness had been hospitalized as a result of his mental health. The trial court based its holding upon the fact that an insufficient basis of good-faith had been shown for the question. The precise form of the question was not quoted in the opinion, so we cannot be sure that it did not imply the impeaching fact — that the witness had been hospitalized. Furthermore, the witness had answered "no" to the question before the objection was sustained, which arguably mooted the analysis. ***In any event, to the extent that Ramirez stands for the proposition that any question pertaining to impeachment must be supported by a reasonable basis for the question, we find it unpersuasive*** [emphasis added].
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> [*P27] Because we conclude that the questions Deaton put to Turner concerning her use of medication at the time of the altercation and at the time of the trial were permitted by Evid. R. 616(B), and were not precluded by Evid. R. 607(B), we conclude that the trial court went outside its discretion when it did not permit them. Because the Confrontation Clause of the Sixth Amendment to the United States Constitution is implicated, we would have to find this error harmless beyond a reasonable doubt. We cannot do so. ***This was essentially a trial that came down to which witness the trial court found more credible — the complaining witness, or the defendant*** [emphasis added]**.** We cannot find, beyond reasonable doubt, that the result of the trial would have been the same had Deaton been permitted to ask Turner about medications she may have been taking. *State v. Deaton*,

Whether rooted directly in the Due Process Clause or in the Compulsory Process or Confrontation clauses of the Sixth Amendment, the Constitution guarantees criminal defendants a meaningful opportunity to present a complete defense. A defendant's Sixth Amendment right to confront the witnesses against him is violated where it is found that a trial judge has limited cross-examination in a manner that precludes an entire line of relevant inquiry.

The impeaching fact that will be implied in Defense Counsel's questioning of the alleged victim is that she suffers from interpersonal difficulties, perhaps rising to the level of a maladaptive disorder. Evid. R. 616(B) permits evidence of "a defect of capacity, ability, or opportunity to observe, remember, or relate, to be shown to impeach a witness." Evid. R. 607(B) provides that "A questioner must have a reasonable basis for asking any question pertaining to impeachment that implies the existence of an impeaching fact."

Here the line of impeachment questioning to be developed from the CFS records goes to defect of capacity, is in good faith, is not violative of Ohio's rape shield or Marsy's law, and conforms with Ohio Evidence Rules 616(B) and 607(B).

III. CFS RECORDS ARE PERMISSIBLE BASIS FOR "WITNESS CHARACTER FOR TRUTHFULNESS" PER OHIO EVIDENCE RULE 608(b)

At its core, Rule 608(b) permits any questions on cross-examination that relate to specific instances of misconduct in the witness's past, so long as the lawyer has a good-faith basis to believe that such instances of misconduct are probative of the witness's character for truthfulness or untruthfulness. The rule's broad scope captures any instances where the witness lied or acted in a dishonest or deceitful way, with no explicit time or substance restrictions. This could include virtually any dishonest conduct in the witness's past, from lying on a job application to failing to file tax returns to more serious allegations of misconduct, like theft or bribery. The conduct need not even amount to a criminal action, as criminal conduct is covered by a separate rule of evidence. ***Therefore, Rule 608(b) opens a wide door to effective and damaging impeachment material*** [emphasis added]. *ABA* **"**A Quick Guide to Rule 608(b): An Underutilized Impeachment Tool."

The CFS records will provide Defense Counsel and his expert a good-faith basis to develop inquiry about the alleged victim's past instances of misconduct to establish her character for truthfulness or untruthfulness.

IV. THE NATURE OF CCDCFS RECORDS

It is long settled both federally and in Ohio that the records of Children Service agencies charged with investigating allegations of child abuse are subject to in-camera inspection and then, if the trial court agrees, available for use by a party. Although a domestic relations court case, *Johnson v. Johnson*, Court of Appeals of Ohio, Third Appellate District, 134 Ohio App. 3d 579, (Union County 1999), provides a detailed overview of the law:

> However, records which are prohibited from being released by state or federal law are excepted from public inspection. See R.C. 149.43(A)(1). For example, in a civil proceeding, records and reports compiled by the Department of Human Services and the Children Services Board regarding allegations of child abuse are confidential and privileged. See R.C. 2151.421(H)(1); 5153.17; *State ex rel. Renfro v.* **[*583]** *Cuyahoga Cty. Dept. of Human Serv.* (1990), 54 Ohio St. 3d 25, 27, 560 N.E.2d 230 (holding that a child abuse report is not a public record and, therefore, is not subject to public inspection).
>
> R.C. 2151.421(H)(1), provides that:
>
> ***[A]*** *report made under this section is confidential*. The information provided in a report made pursuant to this section and the name of the person who made the report shall not be released for use, and shall not be used, as evidence in any civil action or proceeding brought against the person who made the report. In a criminal proceeding, the report is admissible in evidence in accordance with the Rules of Evidence and is subject to discovery in accordance with the Rules of Criminal Procedure. (Emphasis added.)
>
> Thus, R.C. 2151.421(H)(1) clearly removes child abuse or neglect investigation reports from the mandatory disclosure provisions of R.C. 149.43(B). *State ex rel. Renfro, supra.* We also note that the Departments of human services and the children service's board are required to keep records and reports of alleged child abuse or neglect confidential or they face potential criminal charges. See R.C. 2151.99.
>
> The confidentiality of such records and reports is, however, not absolute. Case law, as well as statutory law, have set [**1147] forth a number of exceptions to the confidentiality rule outlined in R.C. 2151.421(H)(1). For example, R.C. 5153.17 states:

"The public children services board or county department of human services shall prepare and keep written records of investigations of families, children, and foster homes, and of the care, training, and treatment afforded children, and shall prepare and keep such other records as are required by the department of human services. *Such records shall be confidential*, *but * * * shall be open to inspection by the agency, the director of the county department of human services, and by other persons, upon the written permission of the executive secretary.* (Emphasis added).

Therefore, pursuant to R.C. 5153.17, although the children's services agency has a duty to keep child abuse records confidential, such confidentiality is not absolute. See, also, *Sharpe v. Sharpe* (1993), 85 Ohio App. 3d 638, 620 N.E.2d 916. However, access to such records will only be granted by the executive secretary on a showing of "good cause." 1991 Ohio Atty.Gen.Ops. No. 91-003. "Good cause" is shown "when it is in the best interests of the child or when the due process rights of other subjects of the record are implicated[.]" *Id.*

Case law has also established several exceptions to the confidentiality rules set forth in R.C. 2151.421(H)(1) and R.C. 5153.17. In the criminal context, the United States Supreme Court has acknowledged that, under certain circumstances, records of the children services agency must be made available to the **[*584]** trial court for an *in camera* inspection. In *Pennsylvania v. Ritchie* (1987), 480 U.S. 39, 94 L. Ed. 2d 40, 107 S. Ct. 989, the United States Supreme Court held that a criminal defendant's right to a fair trial entitles the defendant to an *in camera* review by the trial court of the confidential records in order to determine whether the records contain evidence material to the accused's defense.

Numerous courts throughout Ohio have also acknowledged that, under certain circumstances, records of the children services agency must be made available to the trial court for an *in camera* inspection. In the criminal context, the Fifth District Court of Appeals has held that the confidentiality provision set forth in R.C. 5153.17 is not absolute, and that the proper procedure in determining the availability of such records is for the trial court to conduct an *in camera* inspection to determine the relevancy and necessity of the records, and whether their admission outweighs the confidentiality provisions of R.C. 5153.17. *State v. Fuson*, 1998 Ohio App. LEXIS 4047 (1998), Knox App. No. 97 CA 000023, unreported; *State v. Hart* (1988), 57 Ohio App. 3d 4, 566 N.E.2d 174.

In the juvenile proceeding context, courts throughout Ohio have also granted reasonable access to child abuse files. The Eleventh District Court of Appeals in *Davis v. Trumbull Cty. Children Services Board* (1985), 24 Ohio App. 3d 180, 184, 493 N.E.2d 1011, has held that when children services is relying on records to establish permanent custody through a dependency action, the board must permit the parent reasonable access to the files of the agency in order to obtain information relevant to the issues before the court. In *Davis, supra*, the confidentiality provision set forth in R.C. 5153.17 was overridden by a person's fundamental right to a fair trial.

The Supreme Court of Ohio has also addressed the issue of whether to allow foster parents

the right to inspect a child abuse investigation report. See *State ex rel. Renfro*, 54 Ohio St. 3d 25 at 27, 560 N.E.2d 230. In *Renfro, supra,* the Cuyahoga County Department of Human Services ("CCDH") removed a foster child from her foster parents' home due to suspicions of child abuse. The CCDH used a child [**1148] abuse investigation report as a basis for not returning the foster child to her foster parents. The parents sought a writ of mandamus from the Supreme Court of Ohio compelling the CCDH to make the investigation report available for inspection by the foster parents. The Court, however, refused, holding that the CCDH had no duty to disclose the report.

The facts of the present case, however, are clearly distinguishable from the facts set forth in *Renfro, supra.* In the case *sub judice,* Armstrong has pending before the trial court a motion for a change of custody of her fourteen year-old child.

We note that during the proceedings of August 20, 1998, the trial court stated in pertinent part that:

[*585] I've got a motion here by the mother for custody of a 14-year-old girl, and we know from some of these records that there are allegations that somebody in her household may have been the perpetrator of sexual abuse, and I think it's ludicrous for the Department of Human Services to be telling the Court that we're not going to make this information available to you, and you've got to go ahead and blindly decide that motion, and then if I decide it the wrong way, and abuse later on occurs in the household, then what's the Department of Human Services going to say?

We realize that the child or human services agency's primary responsibility pursuant to R.C. 5153.17 and R.C. 2151.421(H)(1) is to maintain the confidentiality of child abuse records and reports, and we are acutely aware that the rules of confidentiality exist to protect not only the victim--the abused child, but also those who report the alleged abuse. We are also aware that the legislature has provided only limited exceptions to the confidentiality provisions set forth in R.C. 5153.17 and R.C. 2151.421(H)(1).

We are firmly convinced, however, that the importance of maintaining the confidentiality of child abuse records in domestic relations matters may be overridden by more compelling reasons favoring disclosure, such as the great interest in protecting the general health and welfare of a child. In pursuing such an objective, we recognize the long-standing principle that courts "possess inherent power to do all things necessary to the administration of justice * * * ." *Slabinski v. Servisteel Holding Co.* (1986), 33 Ohio App. 3d 345, 346, 515 N.E.2d 1021.

Another case from the Third Appellate Court, *State v. Branch,* Court of Appeals of Ohio, Third Appellate District, 2013-Ohio-3192 (Allen County 2013):

This assignment of error implicates Crim.R. 16(B)(5), which states that a criminal defendant is entitled to the discovery of evidence that is "favorable to the defendant and material to either guilt or punishment." In cases involving child services records, this

> requirement comes into conflict with the confidentiality that attaches to such records pursuant to R.C. 2151.421(H)(1) and R.C. 5153.17. Johnson v. Johnson, 134 Ohio App.3d 579, 583, 731 N.E.2d 1144 (3d Dist. 1999). The United States Supreme Court has resolved this conflict by holding that a defendant's due process right to a fair trial entitles him to an in camera inspection by the trial court of confidential child services records to assess whether they contain evidence that is material to the defendant's guilt. Pennsylvania v. Ritchie, 480 U.S. 39, 60, 107 S.Ct. 989, 94 L. Ed. 2d 40 (1987). We have further defined the rule announced in Ritchie as follows:
>
> [A] court may conduct an in camera inspection of child-abuse records or reports and also has the inherent power to order disclosure of such records or reports where (1) the records or reports are relevant to the pending action, (2) good cause for such a request has been established by the person seeking disclosure, and (3) where admission of the records or reports outweigh the confidentiality considerations set forth in R.C. 5153.17 and R.C. 2151.421(H)(1). (Emphasis sic.) Johnson at 585.

The Defendant has a good cause basis for his request, which make the records relevant, and any consideration for the confidentiality of the matters described in the requested records is far outweighed by the need of the Defendant to defend himself against a potential life sentence.

For all the foregoing legal analysis this court should grant Defendant's Motion to Compel the entire CFS record file in this matter.

/s JAMES SIDNEY JONES (64099)

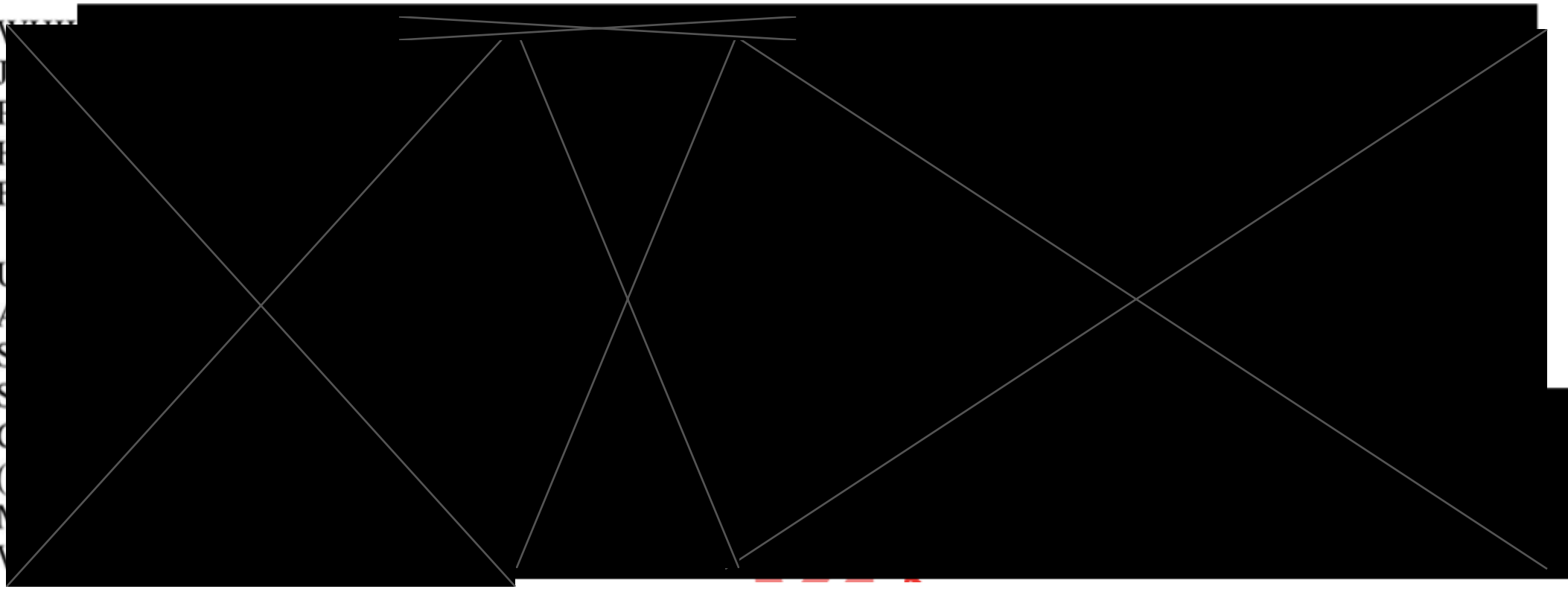
JAMES SIDNEY JONES, LPA
3901 AQUA MARINE BLVD.
AVON LAKE, OH 44012
attorneyjamessidneyjones@gmail.com
(216) 797-9520

CERTIFICATE OF SERVICE

I CERTIFY that a true copy of the above Notice was filed with the CCCP Clerk of Courts this day of , 2022.

/s JAMES SIDNEY JONES (64099)

JAMES SIDNEY JONES, LPA



Adverse Childhood Experiences and Justice System Contact: A Systematic Review

Gloria Huei-Jong Graf, MPH,[a] Stanford Chihuri, MPH,[b] Melanie Blow, BS,[c] Guohua Li, DrPH[a,b]

abstract

CONTEXT: Given the wide-ranging health impacts of justice system involvement, we examined evidence for the association between adverse childhood experiences (ACEs) and justice system contact in the United States.

OBJECTIVE: To synthesize epidemiological evidence for the association between ACEs and justice system contact.

DATA SOURCES: We searched 5 databases for studies conducted through January 2020. The search term used for each database was as follows: ("aces" OR "childhood adversities") AND ("delinquency" OR "crime" OR "juvenile" OR criminal* OR offend*).

STUDY SELECTION: We included all observational studies assessing the association between ACEs and justice system contact conducted in the United States.

DATA EXTRACTION: Data extracted from each eligible study included information about the study design, study population, sample size, exposure and outcome measures, and key findings. Study quality was assessed by using the Newcastle-Ottawa Scale for nonrandomized trials.

RESULTS: In total, 10 of 11 studies reviewed were conducted in juvenile population groups. Elevated ACE scores were associated with increased risk of juvenile justice system contact. Estimates of the adjusted odds ratio of justice system contact per 1-point increase in ACE score ranged from 0.91 to 1.68. Results were consistent across multiple types of justice system contact and across geographic regions.

LIMITATIONS: Most studies reviewed were conducted in juvenile justice-involved populations with follow-up limited to adolescence or early adulthood.

CONCLUSIONS: ACEs are positively associated with juvenile justice system contact in a dose-response fashion. ACE prevention programs may help reduce juvenile justice system contacts and improve child and adolescent health.

[a]*Department of Epidemiology, Mailman School of Public Health and* [b]*Department of Anesthesiology, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York; and* [c]*Stop Abuse Campaign, New York, New York*

Ms Graf helped to conceptualize and design the study, performed initial literature search and screening, performed data extraction and data analyses, and wrote an initial draft of the manuscript; Mr Chihuri helped to conceptualize and design the study, assessed a subsample of screened articles for accuracy, and performed data extraction and data analyses; Ms Blow helped to conceptualize and design the study, coordinated and supervised data collection, and revised and edited manuscript drafts for clarity and intellectual content; Dr Li conceptualized and designed the study, coordinated and supervised data collection, assessed a subsample of screened articles for accuracy, and revised and edited manuscript drafts for clarity and intellectual content; and all authors critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Adverse childhood experiences (ACEs) are a set of childhood adversities, including household dysfunction and various forms of abuse and neglect, occurring before the age of 18.[1] The original ACE study conducted by Kaiser Permanente and the Centers for Disease Control and Prevention included 7 predefined categories of childhood exposures, which have been expanded over time to include a greater number of categories and specific experiences, such as peer victimization and exposure to community violence.[2,3] The ACE pyramid provides a theoretical framework to understand the impact of ACEs on poor health: traumatic childhood experiences influence future health and well-being through a pathway of disrupted neurodevelopment and social, emotional, and cognitive impairment, leading to the adoption of health-risk behaviors and physical and mental health problems, and finally resulting in early death.[4]

Over the past 2 decades, ACEs have emerged as a strong and policy-relevant predictor of morbidity and health-risk behaviors across the life course. The original ACE study, conducted in 1998 by the Centers for Disease Control and Prevention and Kaiser Permanente, found that ACEs are both common and associated with mortality and health-risk behaviors in the general population.[5] Since then, strong associations have continually been identified between ACEs and a wide range of adverse physical and mental health outcomes as well as health-risk behaviors.[6–8]

Childhood trauma has also been linked to excess contact with the justice system, especially among juvenile populations.[9–11] Although much of this work predates the widespread use of the ACEs questionnaire, research on the trauma-crime relationship is often relevant and applicable to the ACE framework. The frequent co-occurrence of delinquency and victimization has been documented, and justice-involved youth who have experienced poly-victimization are more likely to report being involved in delinquency than non–justice-involved youth.[12,13] In multiple studies, authors have estimated that ~25% to 30% of incarcerated youth meet the criteria for posttraumatic stress disorder,[10,14] and children involved with the child welfare system are also overrepresented among justice-involved youth.[14,15] In their 2006 report to the National Bureau of Economic Research, Currie and Tekin[16] found that childhood maltreatment doubled the risk of engaging in self-reported criminal activity. More recently, Layne et al[17] identified graded relationships between the number of traumatic exposures in childhood and high-risk behaviors in later life.

The relationship between trauma and justice involvement is of particular interest to public health given the wide-ranging individual and community impacts of incarceration and policing.[18,19] At the individual level, involvement with the justice system may lead to and exacerbate health disparities in substance use,[20,21] infectious disease,[22,23] mental illness,[20,24] injury,[21,25] chronic disease,[26] and death.[27–29] At the community level, incarceration destabilizes family structures and hampers employment and economic opportunity, political participation, and community stability.[18,30] As such, justice system contact represents an important public health problem as both marker and predictor of poor individual and community well-being. Given the concentration of childhood trauma and justice system involvement in disadvantaged communities, as well as their associated public health impacts, evidence regarding the association of ACEs with justice system contact is potentially helpful for policy makers, those working with justice-involved persons, and public health practitioners alike. In this systematic review, we aim to synthesize epidemiological evidence for the association between ACEs and justice system contact (eg, arrest, conviction, recidivism, and incarceration)—specifically, the graded effects of cumulative ACE score on justice system contact in the United States.

METHODS

We conducted a systematic review of observational studies examining the relationship between cumulative ACE score and justice system contact in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines.[31,32] The review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42020169637).

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (1) exposure was or could be transformed to reflect cumulative ACE score, whether obtained directly from administration of the ACE questionnaire or extracted and calculated from secondary sources (eg, child protective services reports or institutional records); (2) the outcome was related to contact with the justice system (eg, arrest, incarceration, and felony charge) and was verified through third-party records or self-reported (see below); (3) the authors used an epidemiological design (cross sectional, cohort, or case control) and reported quantitative measures of association; and (4) the study was conducted in the United States. No restrictions based on participant incarceration status or publication date were applied. No restrictions on comparator group (or lack thereof) were applied because the primary effect of interest was the graded effect of each 1-point increase in ACE

score. No restrictions were placed on the number or type of ACEs measured in each study. We restricted this systematic review to studies conducted in the United States to reduce heterogeneity resulting from (1) country-level differences in adult and juvenile justice systems[33] and (2) potential differences in ACE prevalence between the United States and other high-income countries,[34] both of which might represent important leverage points for law or policy intervention.

Through the course of the review, it became apparent that some samples of juvenile offenders had rather been adjudicated to alternative treatment facilities; we also included these studies if it was explicitly stated that the outcome of interest was equivalent to or an alternative to arrest or felony charge in a juvenile population. Additionally, there was one modification to the International Prospective Register of Systematic Reviews protocol during the systematic review: whereas studies on criminal behavior (eg, sexual offending and gang involvement) were included only if verifiable through third-party records, contact with law enforcement via arrest or incarceration was deemed eligible if self-reported. The rationale for this modification was twofold: first, contact with law enforcement can theoretically be validated and may be less prone to response bias than criminal activity about which law enforcement is not yet aware; and second, community-based surveys must often rely on self-reported behavior because of practical constraints. Finally, single-item reports of arrest or incarceration are a commonly used outcome measure with acceptable test-retest reliability and validity.[35]

Studies were excluded if (1) the childhood trauma (exposure) measurement was not operationalized as a cumulative ACE score and could not be transformed to a cumulative ACE score; (2) the outcome measure was self-reported criminal behavior that was not verifiable through third-party records (eg, self-reported vandalism, violence, and other delinquent behaviors that did not result in contact with law enforcement); or (3) no quantitative data were reported, such as commentaries, opinion pieces, qualitative studies, letters, editorials, and reviews.

Search Strategy and Information Sources

We searched the following 5 databases from January 24 to January 30: PubMed, PsycINFO, ProQuest, Web of Science, and Google Scholar. The Google Scholar search was limited to the first 200 results; this is consistent with previous literature on optimal search strategy[36] and seeks to balance the sensitivity of Google Scholar's search strategy against the large number of false-positives generated. The search term used for each database was as follows: ("aces" OR "childhood adversities") AND ("delinquency" OR "crime" OR "juvenile" OR criminal* OR offend*).

Study Selection

Initial literature search and screening was performed by a graduate student in epidemiology (G.G.), and a subsample of the screened articles were assessed for accuracy by 2 investigators (G.L. and S.C.) with extensive experience in systematic reviews and meta-analyses. All search results were collected in a central database and deduplicated. Study abstracts were first screened for eligibility; we then reviewed the full text of potentially eligible articles to make a final eligibility determination. Reference lists and related article links of eligible studies were searched to identify additional potential studies for inclusion; the studies were then reviewed and assessed for eligibility.

Data Extraction and Analysis

The following data were extracted from each eligible study independently by 2 of us (G.G. and S.C.): study authors, publication year, journal, sample size, study population, study design, exposure measurement, outcome definition, outcome ascertainment, covariates, subgroups, and measures of effect reported. Discrepancies in the abstracted data were resolved through discussion and consensus building led by the senior author (G.L.). The principal summary measure of interest was the adjusted odds ratio (aOR) for justice system contact given a 1-point increase in ACE score. Where possible, estimates were obtained directly from published articles. Alternatively, estimates were transformed from data presented in the published article; if neither of these was possible, data necessary for these calculations were requested from study authors. When results were reported separately by subgroup (eg, race or sex), data were abstracted separately for each subgroup.

Study quality and risk of bias were assessed by using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies.[37] Cross-sectional studies were evaluated by using a modified NOS that is based on criteria developed by Modesti et al.[38] Given evidence of significant heterogeneity in the studies eligible for review, we present a qualitative synthesis of findings in the present report.

RESULTS

Study Selection

The initial search of 5 databases yielded 544 records; of them, 194 duplicate records were removed, and the remaining 350 titles and abstracts were screened for relevance by the first author. Of the 350 records, 257 were deemed not relevant; the full

text of the remaining 93 records was reviewed for eligibility. Of these 93 records, 71 were excluded for (1) irrelevant study aim (n = 37); (2) incompatible exposure measurement (n = 14); (3) outcome self-reported or otherwise ineligible for inclusion (n = 12); (4) non-US sample (n = 6); and (5) commentaries and review (n = 2). In addition, 11 studies were excluded because of overlapping samples with identical outcome measures. A total of 11 studies were selected for inclusion in the final systematic review (Fig 1).

Study Characteristics

Of the 11 studies evaluating the association between ACE score and justice system contact, 3 reported juvenile arrest as their primary outcome of interest,[39–41] 2 examined sexual offending,[42,43] 2 examined juvenile reoffending,[44,45] 1 examined serious, violent, and chronic delinquency as a juvenile,[46] 1 examined early juvenile offending,[47] 1 examined juvenile gang involvement,[48] 1 examined early adulthood felony charge,[40] and 1 examined adult incarceration.[49] A total of 15 results were included in our primary meta-analysis because of multiple outcomes being reported within a single study,[40] separate reporting of results by Black and white race,[39] and separate reporting of results by sex[42,45] (Table 1).

Study Quality

Eight of the 11 eligible studies adjusted for important covariates including race, sex, community and neighborhood factors, and risk behaviors. Of the 3 studies that did not, the absence of covariate adjustment in 2 studies was explained by the need for data transformation to assess the primary relationship of interest.[42,43] The average Newcastle-Ottawa Score for cohort studies was 7.75 of 9 (range 7–8), with most studies losing 1 point because of a lack of sample representativeness. In the NOS adapted for cross-sectional studies, the average score was 7.2 of 10 (range 5–9). Among all studies, only 1 was performed in a representative state community sample[49]; all other studies were conducted in juvenile populations (n = 7), in samples of children at high risk for maltreatment (n = 2), or in an adult population with a history or violent or sexual offenses (n = 1). In 7 studies, researchers used comprehensive data from state juvenile justice populations; 1 study used a state community sample; 2 studies used "high-risk" samples in selected US cities; and 1 study used a sample drawn from an inpatient treatment facility. Notably, data from the Florida Department of Juvenile Justice (n = 6) were overrepresented among included studies. Ascertainment of exposure and outcome measurements were generally strong because of stringent inclusion criteria in the present review. Assessments of study quality are available in Supplemental Tables 2 and 3.

Summary of Findings

Of the 15 results from 11 studies included in our primary analysis, 13 revealed statistically significant positive associations between ACE score and justice system contact, whereas 2 indicated no significant association[39,40] (Fig 2). The estimated aORs for justice system involvement ranged from 0.91 to 1.68 per 1-point increase in ACE score. In most studies (10 of 11) included in our review, authors examined outcomes in youth and young adulthood. We found that a 1-point increase in ACE score is associated with 9% lower to 68% higher odds of juvenile justice system contact. Further research is needed to reliably summarize the relationship between ACE score and justice system contact in adulthood and later life.

In 7 out of the 10 studies examining juvenile outcomes, authors examined outcomes in statewide juvenile populations,[42–48] increasing confidence in the validity of our primary findings. Results were consistent in the direction of association and significance across geographic regions within the United States.

DISCUSSION

We found compelling and consistent epidemiological evidence for a graded relationship between ACE score and juvenile justice system contact in the United Status. However, estimates of the overall relationship between ACE score and justice system contact across the life course were limited by the lack of studies in which authors examined adult justice involvement and should be interpreted with caution. Because the ACE framework explicitly takes a life course perspective, the association between ACE score and justice system contact in adulthood and later life is a promising area for future investigation. An understanding of the life course impacts of ACEs on justice system contact is important for policy makers and pediatric providers alike given the potential long-ranging impacts of intervening on these exposures in childhood.

Our findings support previous research identifying links between childhood trauma and subsequent contact with the justice system.[14,16,17] Alongside previous literature linking both ACEs and incarceration to poor health, these findings provide empirical support for the relationship between ACE exposure and justice system contact. Further research is needed to assess the pathways through which victimization leads to justice system contact and how each of these in turn may contribute to poor health, including relationships between victimization and perpetration[12] and behavioral and mental health risks of victimization.[13]

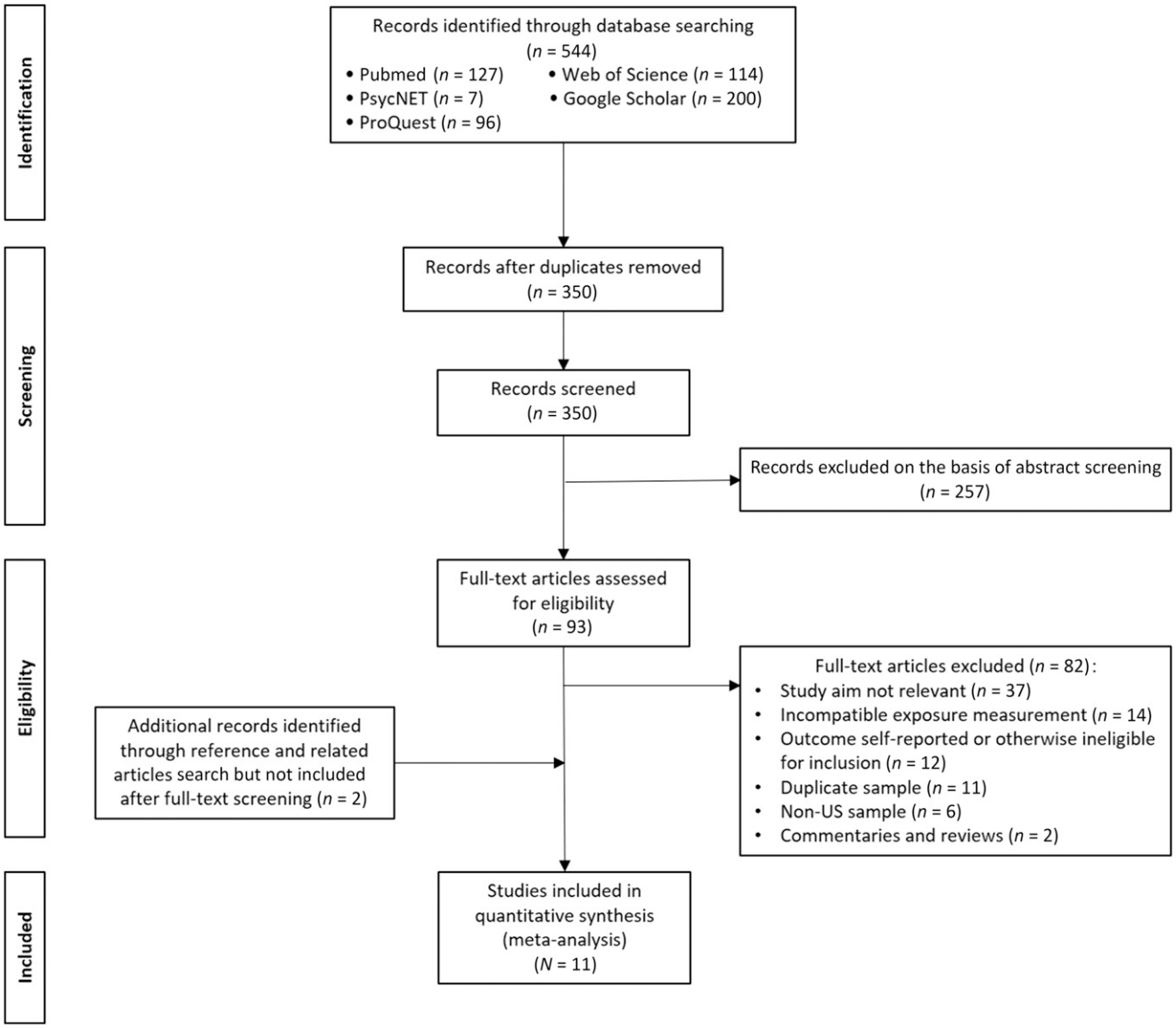

FIGURE 1
Flowchart: identification, review, and selection of studies related to the graded effect of ACEs on justice system contact. Adapted from Moher et al.[31]

Our findings in this review are particularly salient to pediatric providers for several reasons. First, given evidence of associations between ACEs and juvenile justice involvement, pediatric providers may oversee patients both at the time of exposure (experience of ACEs) and outcome (justice system contact). Thus, pediatric providers represent an important stakeholder in interventions targeting both exposure and subsequent risk of justice system involvement. Second, the ACE framework identifies childhood as a highly susceptible period, during which exposure to adverse experiences "gets under the skin" to affect outcomes across the life course. Thus, intervention or guidance by pediatric providers during this critical period can potentially have benefits far beyond childhood and adolescence.

In the course of our review, we identified evidence of publication bias and significant heterogeneity across the studies reviewed. The publication bias issue may be mitigated by characteristics of the studies included in this review: 8 of 11 studies were in large data sets (range: 13 803–104 266 participants), all of which were population samples of juvenile offenders at the state level. It is common to find significant heterogeneity in outcomes of observational studies partly because of differences in the study designs, study samples, analytical approaches, and confounding factors controlled for. As more evidence becomes

TABLE 1 Characteristics of Studies Included in Meta-analysis of Graded Effects of ACEs on Justice System Contact

Author, y	Data Source	Population	*N*	Study Design and/or Analysis	Study Time Period	No. ACEs Captured (Age Range): ACEs Captured (Exposure Assessment)	Outcome and Definition	Outcome Ascertainment	Covariates	Key Finding(s)
Baglivio et al,[47] 2015	FDJJ archival data records	All youth in Florida with an arrest history who were administered the full C-PACT and turned 18 during the study period	64 329	Cohort, logistic regression	January 1, 2007–December 31, 2012	10 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, family violence, household substance abuse, household mental illness, parental separation or divorce, household member incarceration score transformed from C-PACT items (administered through a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)	Membership in juvenile offending trajectory group; we extracted data on early starters compared with mid- to early starters who later desist.	JJIS data extracts were used to gather every instance of arrest for youth at each age up to age 17.	Race, sex	Each 1-point increase in ACE score was associated with a 28.7% increase in the odds of being an early starter relative to the odds of being a mid- to early starter who later desists.
Craig,[44] 2019	FDJJ archival data records	3-y cohort of all youth with an arrest history who completed some form of a community-based placement during the study period	25 461	Cohort, logistic regression	July 1, 2009–June 30, 2012	10 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, household substance abuse, violent treatment toward mother, parental separation or divorce, household mental illness, household member incarceration score transformed from C-PACT items (administered through a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)	Reoffending, defined as rearrest within 12 mo after completion of community-based placement	Arrest records were from FDJJ.	Race, sex, age, disadvantage, additional covariates related to antisocial peer associations, impulsivity, social bonds, youth criminal history and criminal attitudes	Each 1-point increase in ACE score was associated with a 3% increase in the odds of 12-mo rearrest.
Fagan and Novak,[39] 2018: (1) Black participant; (2) white participants	LONGSCAN study of child maltreatment (Baltimore, Chicago, San Diego, Seattle, Chapel Hill)	High-risk sample of children ages 4–6 and caregivers (based on having a history of maltreatment or considered at risk for based on parents' low SES and maternal substance use)	620	Cohort, logistic regression	1990–2002	10 (before age 12): emotional abuse, physical abuse, sexual abuse, failure to provide (ie, physical neglect), lack of supervision, caregiver intimate partner violence victimization, caregiver depression, caregiver substance use or abuse, caregiver criminality, family trauma transformed from child protective services agency records from states participating in LONGSCAN (based on child and caregiver responses to Modified Maltreatment Classification System and Conflict Tactics Scale; cumulative ACE score was winsorized at 7)	Past-year arrest at age 16	Self-reported, primary caregiver reports	Age, sex, single parent, geographic region, poverty, other neighborhood and community covariates; analyses stratified by race	Among Black participants, each 1-point increase in ACE score was associated with a 23% increase in the odds of past-year arrest at age 16. Findings were not significant for white participants (aOR 0.91; 95% CI [0.69–1.20]).

TABLE 1 Continued

Author, y	Data Source	Population	*N*	Study Design and/or Analysis	Study Time Period	No. ACEs Captured (Age Range): ACEs Captured (Exposure Assessment)	Outcome and Definition	Outcome Ascertainment	Covariates	Key Finding(s)
Fleming and Nurius,[49] 2019	Washington state BRFSS survey (2011)	State implementation of nationally representative survey conducted in collaboration with the CDC	13 803	Cross-sectional, Wald difference test	2011	8 (before age 18): sum of participant responses to 8 CDC categories of ACEs: emotional abuse, physical abuse, sexual abuse, household incarceration, living with someone with serious mental illness, living with someone with substance use issues, parents divorced or separated, parents who physically hurt one another	Adult incarceration (after age 18)	Self-reported	Race, sex, education	Findings after data transformation: each 1-unit increase in ACE score was associated with an 18% increase in the odds of adult incarceration.
Giovanelli et al,[40] 2016: (1) outcome: juvenile arrest; (2) outcome: adult felony charge	Chicago Longitudinal study	Low-income, minority sample born in high-poverty neighborhoods in Chicago from 1979 to 1980	1200	Cohort, logistic regression	1986 (start of study) to 2002 (age 22–24 follow-up survey)	9 (before age 18): physical abuse, sexual abuse, neglect, prolonged absence of parent or divorce of parents, death of family member or close friend or relative, frequent family conflict, problems of substance abuse of parent, witness to a shooting or stabbing, violent crime victimization (assessed in survey at 22–24 y; physical abuse, sexual abuse, and neglect items obtained from administrative records)	Two outcomes: (1) juvenile arrest (ages 10–18) and (2) felony charge (ages 18–24)	Juvenile arrest records were obtained from petitions to Cook County Juvenile Court and 2 other Midwestern locations. Felony charges were taken from federal prison records as well as documented histories in state, county, and circuit courts.	Race, sex, family ecology of risk, CPC intervention status	Findings after data transformation: each 1-unit increase in ACE score was associated with a 13% increase in the odds of juvenile arrest. Findings were not significant for felony charge (aOR 1.04; 95% CI [0.97–1.12]).
Kowalski,[45] 2019: (1) male participants; (2) female participants	Archival records from juvenile justice agency in Washington state	Youth on probation in Washington state who completed the PACT full assessment during the study period	35 442	Cohort, logistic regression	December 2003–June 2017	10 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, domestic violence, household substance abuse, household mental health problems, parental separation or divorce, incarceration of a household member score transformed from C-PACT items (administered through a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)	Reoffending, defined as a new felony, misdemeanor, violent, property, drug, or sex offense at 12 mo	Records were from Washington state (standard 18-mo follow-up period).	Race, sex, age, mental health status, substance use, risk level	Among male participants, each 1-point increase in ACE score was associated with a 7% increase in the odds of 12-mo reoffending. Among female participants, each 1-point increase in ACE score was associated with a 4% increase in the odds of 12-mo reoffending.
Levenson et al,[42] 2017: (1) male participants; (2) female participants	FDJJ archival data records	Youth who aged out of the juvenile justice system (turned 18 y old) and who were assessed with the C-PACT full assessment during the study period	89 045	Case control, logistic regression	January 1, 2007–December 31, 2015	10 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, family violence, household substance abuse, household mental illness, parental separation or divorce, household member incarceration score transformed from C-PACT items (administered through	Juvenile sexual offending (misdemeanor or felony offenses), defined as arrest ≥1 time for a sexual offense before age 18	Arrest records were from FDJJ.	None	Findings after data transformation: among male participants, each 1-point increase in ACE score is associated with a 1% increase in the odds of juvenile sexual offending versus nonsexual offending. Among female participants, each 1-unit increase in ACE score is associated with a 4% increase in the odds of

TABLE 1 Continued

Author, y	Data Source	Population	*N*	Study Design and/or Analysis	Study Time Period	No. ACEs Captured (Age Range): ACEs Captured (Exposure Assessment)	Outcome and Definition	Outcome Ascertainment	Covariates	Key Finding(s)
						a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)				juvenile sexual offending versus nonsexual offending.
Naramore et al,[45] 2017	FDJJ archival data records	All youth in Florida ages with an arrest history who were administered the full C-PACT and were 11.4–22.5 y at the time of their last assessment	64 329	Cross sectional, logistic regression	December 14, 2005–December 30, 2012	10 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, family violence, household substance abuse, household mental illness, parental separation or divorce, household member incarceration score transformed from C-PACT items (administered through a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)	Arrest for trading sex (ie, "offer to commit, or to commit, or to engage in, prostitution, lewdness, or assignation" or "aid, abet, or participate in any of the acts or things enumerated in this subsection"[45])	Arrest records were from FDJJ.	None	Findings after data transformation: each 1-point increase in ACE score is associated with a 68% increase in the odds of being arrested for trading sex compared to arrest for other offenses.
Perez et al,[46] 2018	FDJJ archival data records	Youth who aged out of the juvenile justice system (turned 18 y old) and who were assessed with the C-PACT full assessment during the study period	64 329	Case control, logistic regression	January 1, 2007–December 31, 2012	9 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, witnessing household violence, household substance abuse, household mental illness, household member incarceration score transformed from C-PACT items (administered through a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)	SVC delinquency, defined as committing ≥3 serious felony offenses, with at least 1 violent offense	Arrest records were from FDJJ.	Race, sex, SES	Each 1-point increase in ACE score is associated with a 30% increase in the odds of a juvenile offended being classified as an SVC offender.

TABLE 1 Continued

Author, y	Data Source	Population	*N*	Study Design and/or Analysis	Study Time Period	No. ACEs Captured (Age Range): ACEs Captured (Exposure Assessment)	Outcome and Definition	Outcome Ascertainment	Covariates	Key Finding(s)
Stinson et al,[41] 2016	Inpatient forensic psychiatric facility in the Midwestern United States	Selected participants had commitments for violent or sexual offending and a length of admission ≥1 y at the time of data collection of 2 nonoverlapping time samples in 2007 and 2012.	381	Cross sectional, logistic regression	2007, 2012	6 (during developmental years): verbal and/or emotional abuse, physical abuse, intrafamilial sexual abuse, extrafamilial sexual abuse, neglect, parental substance abuse (coded from the social service reports generated at admission and annually by facility personnel; experiences were self-reported by clients, reported by corroborating family members, and/or records obtained from state investigations of reported maltreatment)	Juvenile arrest, defined as arrest before age 19	Available social service records	None	Each 1-point increase in ACE score is associated with 34% higher odds of juvenile arrest among violent and sexual offenders.
Wolff et al,[48] 2020	FDJJ archival data records	Youth who aged out of the juvenile justice system (turned 18 y old) and who were assessed with the C-PACT full assessment during the study period but who were not involved with a gang at time of first assessment and who had information on race and/or ethnicity	104 266	Cohort; rare-events logistic regression	January 1, 2007–December 31, 2017	10 (ever): emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, family violence, household substance abuse, household mental illness, parental separation or divorce, household member incarceration score transformed from C-PACT items (administered through a semistructured interview conducted by a trained juvenile probation officer or contracted assessment staff; additional review of case file and education and child abuse records)	Verified gang involvement; only youth for whom there exists written documentation from law enforcement certifying them as gang involved (as per state statute) were classified as verified.	Law enforcement documentation	Race, sex, age	Each 1-point increase in ACE score is associated with 14% higher odds of gang association among juvenile offenders.

BRFSS, Behavioral Risk Factor Surveillance System; CDC, Centers for Disease Control and Prevention; CI, confidence interval; C-PACT, Community Positive Achievement Change Tool; FDJJ, Florida Department of Juvenile Justice; JJIS, xxx; LONGSCAN, Longitudinal Studies on Child Abuse and Neglect; PACT, Positive Achievement Change Tool; SES, socioeconomic status; SVC, serious, violent, and chronic.

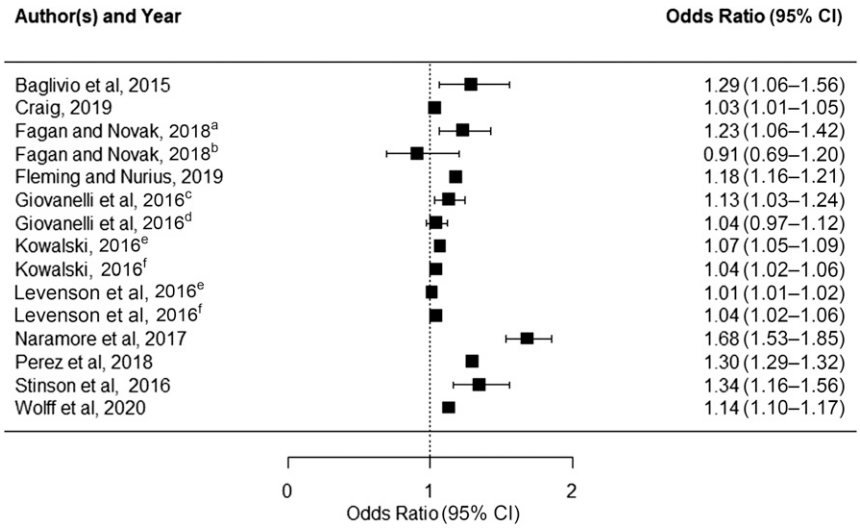

FIGURE 2

Forest plot, estimated aORs, and 95% confidence intervals (CIs) of the association between each 1-point increase in ACE scores and overall justice system contact. [a] Black participants. [b] White participants.[c] Outcome: juvenile arrest. [d] Outcome: adult felony charge. [e] Male participant. [f] Female participant.

available, quantitative synthesis of the association between ACE score and various forms of justice system involvement may be of particular interest.

There are several important considerations that should be raised in light of our findings. First, both ACEs and contact with the justice system in the United States are patterned by socioeconomic factors.[50–52] In the Fagan and Novak[39] study included in our review, results were significant for Black participants but not for white participants. Further research is needed to evaluate the consistency of effect-size differences by race and should consider whether and how overpolicing of economically disadvantaged areas may confound observed associations between ACEs and justice system contact. As the prevalence of ACEs in the United States changes over time,[34] it is also important to observe whether disparities in prevalence and associations with justice system context persist. Assessment of the ACE–justice system relationship by sociodemographic factors in other countries may also serve to identify US-specific drivers of observed disparities.

Second, the generalizability of our findings may be limited because most studies in this review examined justice-involved or underresourced populations. Although the original ACE study was conducted in a predominantly white, college-educated sample with private health insurance, subsequent studies have established strong associations between trauma and poor health in minority and disadvantaged populations.[53–57] In a 2006 report, Currie and Tekin[16] found that the effects of trauma were found to be particularly harmful to children from low socioeconomic status families. Effect-size estimates from this review may therefore be larger than the true effects in the general population.

However, our findings are in line with a large body of literature identifying negative life course health consequences of ACE exposure across demographic characteristics and socioeconomic context.[5,6] Given unequal ACE distributions by race, sex, and sexual orientation[50] and strong gradients by childhood socioeconomic status,[58] research on ACEs alongside other markers of economic and social disadvantage is of particular importance. Particular attention should be paid to pathways through which these factors intersect with ACEs and justice system involvement in affecting health outcomes in adulthood and later life. Finally, in 9 of 11 studies included in this review, authors calculated the exposure of interest, ACE score, on the basis of a review of existing files or records. Further research is needed to confirm that these findings hold when ACEs are self-reported through the original ACE questionnaire.

Overall, we find epidemiological evidence to support the hypothesis that ACE score is positively and significantly associated with the risk of juvenile justice system contact. Although further research is needed to confirm these associations in older populations, study findings are in line with existing theory regarding the pathways through which ACEs affect health outcomes across the life course. Adding to the existing literature about the impact of ACEs on health and health behaviors across the life course, our findings indicate that targeting ACEs may have positive impacts on individual and community health through the reduction of contact with the justice system, particularly in adolescence and young adulthood.

ABBREVIATIONS

ACE: adverse childhood experience
aOR: adjusted odds ratio
NOS: Newcastle-Ottawa Scale

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Address correspondence to Gloria Huei-Jong Graf, MPH, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 W 168th St, New York, NY 10032. E-mail: gloria.hu@columbia.edu

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Borderline personality disorder and childhood trauma: exploring the affected biological systems and mechanisms

Nadia Cattane[1], Roberta Rossi[2], Mariangela Lanfredi[2] and Annamaria Cattaneo[1,3,4*]

Abstract

Background: According to several studies, the onset of the Borderline Personality Disorder (BPD) depends on the combination between genetic and environmental factors (GxE), in particular between biological vulnerabilities and the exposure to traumatic experiences during childhood. We have searched for studies reporting possible alterations in several biological processes and brain morphological features in relation to childhood trauma experiences and to BPD. We have also looked for epigenetic mechanisms as they could be mediators of the effects of childhood trauma in BPD vulnerability.

Discussion: We prove the role of alterations in Hypothalamic-Pituitary-Adrenal (HPA) axis, in neurotrasmission, in the endogenous opioid system and in neuroplasticity in the childhood trauma-associated vulnerability to develop BPD; we also confirm the presence of morphological changes in several BPD brain areas and in particular in those involved in stress response.

Summary: Not so many studies are available on epigenetic changes in BPD patients, although these mechanisms are widely investigated in relation to stress-related disorders. A better comprehension of the biological and epigenetic mechanisms, affected by childhood trauma and altered in BPD patients, could allow to identify "at high risk" subjects and to prevent or minimize the development of the disease later in life.

Keywords: Borderline personality disorder, Childhood trauma, HPA axis, Endogenous opioid system, Neurotransmission, Neuroplasticity, Neuroimaging studies, Epigenetic mechanisms

Background

Borderline Personality Disorder (BPD) is a pervasive pattern of emotional dysregulation, impulsiveness, unstable sense of identity and difficult interpersonal relationships [1]. The prevalence rates of BPD are between 0.2–1.8% in the general community, 15–25% among psychiatric inpatients and 10% of all psychiatric outpatients [2, 3]. Among the different aetiopathological theories that have been proposed over years, the most supported is the one proposed by Linehan in 1993 [4], which suggests that BPD can be the result of the interactions between biological and psychosocial factors [2], in particular between biologically based temperamental vulnerabilities and adverse and traumatic experiences during childhood.

BPD is a disorder primarily characterized by emotion dysregulation and indeed, patients with BPD show heightened emotional sensitivity, inability to regulate intense emotional responses, and a slow return to emotional baseline. Linehan proposed also that the development of BPD occurs within an invalidating developmental context characterized by intolerance toward the expression of private emotional experiences during childhood [4]. As a consequence, children exposed to this adverse environment show inability to learn how to understand, label, regulate, or tolerate emotional responses and, conversely, they vacillate between emotional inhibition and extreme emotional lability.

Recently, Hughes and colleagues [5] have proposed an integration to the aethiopathogenetic model of BPD,

* Correspondence: annamaria.cattaneo@kcl.ac.uk; acattaneo@fatebenefratelli.eu
[1]Biological Psychiatry Unit, IRCCS Istituto Centro San Giovanni di Dio - Fatebenefratelli, via Pilastroni 4, Brescia, Italy
[3]Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College London, 125 Coldharbour Lane, London SE5 9NU, UK
Full list of author information is available at the end of the article

emphasizing the role played by a lack of social proximity or responsiveness from relevant caregivers in the development of BPD symptoms, which in turn impairs the individual's emotion regulation. Affect regulation difficulties have been also proposed as key mediators in the relationship between childhood trauma and BPD [6].

Several studies have shown that a diagnosis of BPD is associated with child abuse and neglect more than any other personality disorders [7, 8], with a range between 30 and 90% in BPD patients [7, 9].

Adverse childhood experiences are also related to BPD symptom severity [9–11]. In support to this, Widom and collaborators [12] followed 500 children who had suffered physical and sexual abuse and neglect and 396 matched controls, and they observed that significantly more abused/neglected children met criteria for BPD in adulthood in comparison to controls. However, the presence of a risk factor, such as adverse childhood events, was not necessary or sufficient to explain the reason why some individuals developed BPD symptoms in adulthood, whereas others did not.

In a recent study, Martin-Blanco and collaborators [10] have hypothesized that the interaction of childhood trauma and temperamental traits could be associated with the severity of BPD. In this regard, they have evaluated the self-reported history of trauma, the psychobiological temperamental traits and the severity of the BPD symptoms in a cohort of 130 BPD patients. Data showed a correlation only between childhood maltreatment and sociability and no other correlation was observed. Moreover, the interaction between high neuroticism-anxiety traits and the presence of severe emotional abuse was associated with the severity of the disorder.

Symptom overlap has been reported between BPD diagnosis and other disorders including Post-Traumatic Stress Disorder (PTSD) and other axis I disorders [13]. Moreover, in recent decades, different nosographic descriptions have been suggested to characterize the different symptoms associated with trauma, like complex Post-Traumatic Stress Disorder (cPTSD) [14], also known as Disorders of Extreme Stress Not Otherwise Specified (DESNOS) [15], which describes a clinical syndrome following an experience of interpersonal traumatic victimization and shares many similarities with BPD, including pathological dissociation, somatizations, dysregulation of emotions, altered central self and relational schemas. The definition of cPTSD therefore refers to the experience of severe and/or prolonged traumatic situations, and does not merely identify the effects of devastating traumatic events (like violence or chronic maltreatment), which fall under the category of PTSD or Acute Stress Disorder. Indeed, exposure to particular types of traumatic experiences may result in far more insidious and crippling psychopathogenic disorders than PTSD, compromising the sound development of attachment behavior related systems and of the ability to modulate emotions [16]. Recent research is currently trying to determine whether cPTSD and BPD diagnosis in comorbidity with PTSD are distinct or should both be considered and named as trauma-related disorders [17]. A recent review [18] has explored the mechanisms through which childhood trauma is related to the development of BPD in adulthood, and has discussed how interrelated factors (such as heritable personality traits, affect regulation and dissociation, trauma symptoms) could be mediators in the relationship between childhood trauma and BPD.

Based on all these findings, in the following paragraphs we will discuss alterations in several neurobiological systems and in brain morphology that can be induced by exposure to early life adverse experiences and that are also associated with BPD (see Table 1). We will examine the impact of early stressful events on different biological systems and mechanisms, possibly identifying biomarkers that could be involved in BPD vulnerability. This might allow to identify at high risk BPD subjects earlier, and to develop intervention strategies and programs.

Discussion

Neurobiological mechanisms involved in BPD

BPD and the hypothalamic-pituitary-adrenal axis

The Hypothalamic-Pituitary-Adrenal (HPA) axis is one of the neuroendocrine systems which mediate the response of the body to stress. Although the stress response mechanism is meant to maintain stability or homeostasis, its long-term activation, as consequence of chronic stress exposure, may have deleterious effects on the body, increasing the risk for developing different kinds of illnesses, including stress-related psychiatric disorders.

In stress conditions, corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) are released from the paraventricular nucleus (PVN) located in the hypothalamus. These peptides travel through the pituitary portal system and act synergistically to stimulate the release of the adrenocorticotropic hormone (ACTH) from the corticotroph cells. Then, ACTH is transported throughout the systemic circulation and binds to receptors in the adrenal cortex of the adrenal gland, resulting in the biosynthesis and release of cortisol [19]. Cortisol can affect multiple organs and biological processes, such as metabolism, growth, inflammation, cardiovascular function, cognition, and behavior [20, 21], by binding to specific receptors in the body and in several brain regions, as the hypothalamus, anterior pituitary and medial prefrontal cortex. The central and peripheral effects of cortisol are mediated by two intracellular glucocorticoid receptor subtypes: the high-affinity type I receptor or

Table 1 Summary of the papers cited in the review and showing alterations in different biological systems in BPD

Biological systems	Authors	Sample size	Date of study	Main Results
HPA axis	Southwick et al. [26]	37 subjects with PTSD comorbid with BPD; 18 subjects only with PTSD	2003	Higher 24 h urinary cortisol levels in patients with PTSD compared to patients with PTSD and comorbid BPD.
	Wingenfeld et al. [27]	21 female patients with BPD; 24 healthy female controls.	2007	Higher overnight urinary cortisol levels in BPD patients compared to controls. Very high cortisol levels were found only in BPD patients with a low number of PTSD symptoms.
	Rinne et al. [28]	39 BPD patients (24 with and 15 without sustained childhood abuse and comorbid PTSD (n = 12) or MDD (n = 11)); 11 control subjects	2002	Higher ACTH and cortisol levels in the blood of BPD females who had experienced childhood abuse during the DEX/CRH test.
	Carvalho Fernando et al. [29]	32 female BPD patients; 32 healthy female	2013	Acute cortisol levels decreased the reaction time to target stimuli in both BPD patients and controls.
	Martin-Blanco et al. [30]	481 subjects with BPD; 442 controls	2016	Case-control study focusing on 47 SNPs in 10 HPA axis genes. An association between polymorphic variants within the FKPB5 and the CRHR genes with the diagnosis of BPD was shown. Two FKBP5 SNPs were more frequently represented in patients with a history of childhood trauma.
Neurotransmission	Wagner et al. [42]	159 BPD patients	2009	Association between stressful events and low impulsivity in BPD patients. 5-HTTLPR S-allele carriers showed higher impulsivity scores when exposed to stressful events than LL omozygotes.
	Wagner et al. [47]	112 female BPD patients	2010	COMT Val158Met SNP was associated with early life stressful events and impulsive aggression in female BPD patients
	Wagner et al. [48]	159 BPD patients	2010	The effect of COMT Val158Met SNP on the association between stressful life events and impulsivity was not confirmed.
	Tadic et al. [49]	161 Caucasian BPD patients; 156 healthy controls.	2009	The COMT Met158Met SNP was over-represented in BPD patients compared to controls. No differences in 5-HTTLPR genotype were found. An interaction between the COMT Met158 and the 5-HTTLPR s-allele was observed.
	Martin-Blanco et al. [50]	481 BPD subjects; 442 controls	2015	Genetic variants within COMT, DBH and SLC6A2 genes were associated with an enhanced risk to develop BPD
Endogenous Opioid System	Kalin et al. [57]	8 infant rhesus monkeys (4 males and 4 females)	1988	The endogenous opioid system mediates separate-induced vocalizations and influences the HPA axis activation in rhesus monkeys using the mother-infant separation paradigm.
	Prossin et al. [61]	18 un-medicated female BPD patients; 14 female controls	2010	BPD patients had greater regional μ-opioid availability at baseline in the left necleus accumbens, the hypothalamus and the right hippocampus/parahippocampus relative to controls, showing an endogenous opioid system activation.
Neuroimaging studies	Driessen et al. [36]	21 female BPD patients; 21 female controls	2000	Volume reduction in the hippocampus and in the amygdala in BPD patients compared to controls.
	Schmahl et al. [38]	25 unmedicated female patients with BPD (10 with and 15 without comorbid PTSD); 25 female controls	2009	Hippocampal volume reduction in patients with BPD and comorbid PTSD as compared to controls.

Table 1 Summary of the papers cited in the review and showing alterations in different biological systems in BPD *(Continued)*

	Kreisel et al. [70]	39 BPD patients; 39 controls	2014	Smaller hippocampal volume in BPD patients with a lifetime history than those without comorbid PTSD.
	Boen et al. [71]	18 women with BPD; 21 controls	2014	Two hippocampal structures (DG-CA4 and CA2–3 subfields) were significantly smaller in patients with BPD than controls.
	Kuhlmann et al. [73]	30 BPD patients; 33 controls	2013	Patients with BPD showed lower hippocampal volumes than controls, but higher volumes in the hypothalamus.
	Rodrigues et al. [63]	124 BPD patients; 147 controls	2011	Both the left and the right sides of the hippocampus were reduced in BPD patients with PTSD when compared to controls.
	Ruocco et al. [37]	205 BPD patients; 222 controls	2012	Bilateral volume reductions of the amygdala and hippocampus were not related to comorbid MDD, PTSD or substance use disorders.
Epigenetics	Martin-Blanco et al. [88]	281 subjects with BPD	2014	An association between NR3C1 methylation levels and childhood trauma was found in blood samples of BPD patients.
	Dammann et al. [89]	26 BPD patients; 11 controls	2011	An increase in the methylation levels of HTR2A,NR3C1,MAOA,MAOB and COMT was found in BPD patients as compared to controls.
	Perroud et al. [91]	346 BD, BPD, and ADHD patients	2016	Differential 5-HT3AR methylation levels were associated with the severity of childhood trauma, mainly found in BPD patients.
	Teschler et al. [93]	24 female BPD patients; 11 female controls	2013	Genome-wide methylation analyses revealed increased methylation levels of several genes (APBA2,APBA3,GATA4,KCNQ1,MCF2,NINJ2, TAAR5) in blood of BPD female patients and controls.
	Prados et al. [94]	96 BPD subjects suffering from a high level of child adversity; 93 subjects suffering from MDD and reporting a low rate of child maltreatment	2015	Several CpGs within or near genes involved in inflammation and in neuronal excitability were differentially methylated in BPD patients compared to MDD patients or in relation to the severity of childhood trauma.
	Teschler et al. [95]	24 female BPD patients; 11 female controls	2016	A significant aberrant methylation of rDNA and PRIMA1 was revealed for BPD patients using pyrosequencing. For the promoter of PRIMA1, the average methylation of six CpG sites was higher in BPD patients compared to controls. In contrast, the methylation levels of the rDNA promoter region and the 5′ETS were significantly lower in patients with BPD compared to controls.
Neuroplasticity	Koenigsberg et al. [109]	24 medication-free BPD patients; 18 healthy control subjects	2012	Decrease of PKC and BDNF protein levels in the blood of BPD patients.
	Tadic et al. [49]	161 Caucasian BPD patients; 156 healthy controls.	2009	Association between HTR1B A-161 variant and the functional BDNF 196A allele in BPD patients.
	Perroud et al. [90]	115 subjects with BPD; 52 controls	2013	Higher methylation levels in BDNF CpG exons I and IV in BPD patients than in controls. Higher BDNF protein levels in plasma of BPD patients than in controls.
	Thaler et al. [92]	64 women with bulimia nervosa and comorbid BPD; 32 controls	2014	Hypermethylation within BDNF promoter region sites in women with bulimia nervosa and with a history of BPD and/or trauma events.

mineralcorticoid receptor (MR) and the low-affinity type receptor or glucocorticoid receptor (GR). It has been suggested that MRs have a high affinity for both cortisol and aldosterone; they bind cortisol when it is detectable at low concentrations. The GRs have a relatively low affinity for cortisol, but high affinity for dexamethasone (DEX) [22]; moreover, they bind cortisol at high concentration, reflecting what occurs in stress conditions.

The HPA axis is regulated by an auto-regulatory mechanism mediated by cortisol itself, that is crucial in the maintenance of the homeostatic functions of the HPA axis. Indeed, when cortisol levels rise, as in

response to stress, the MRs are saturated and, consequently, cortisol binds the GRs, promoting a cascades of events that represent the main transduction signals of glucocorticoids in stress conditions.

So far, the HPA axis activity has been widely investigated in the context of childhood trauma experiences and findings support alterations in HPA axis in subjects exposed to stress early in life. Indeed, several studies have reported alterations in the cortisol circadian rhythm and levels, indicating a deregulation of the HPA axis responsiveness, due to childhood trauma experiences, upon stress conditions [23–25].

Despite the large amount of data on the HPA axis functionality as consequence of exposure to stress early in life, only a few studies have investigated possible alterations of this axis in BPD patients. For example, higher urinary cortisol levels have been found in BPD patients compared to controls [26, 27].

Southwick and colleagues [26] found higher 24 h urinary cortisol levels in patients with PTSD compared to patients with PTSD and comorbid BPD, suggesting that these alterations might reflect differences in the severity of PTSD symptoms rather than factors related to BPD per se.

Another study [27] explored overnight urinary free cortisol levels showing higher cortisol levels in BPD patients than in controls. A negative association between cortisol and PTSD symptoms was also observed. Moreover, when BPD patients were divided according to the presence of high or low number of PTSD symptoms, very high cortisol levels were found only in BPD patients with a low number of PTSD symptoms. Rinne and collaborators [28] found an exaggerated ACTH and cortisol response during the DEX/CRH test in the blood of BPD female subjects who had experienced childhood abuse. Carvalho Fernando and colleagues [29] investigated the effects of cortisol administration on response inhibition of emotional stimuli in patients with BPD compared to controls. They found that acute cortisol elevations decreased the reaction time to target stimuli in both BPD patients and controls, but they did not differ in task performance.

Also genetic association studies support alterations in HPA axis functionality in association with childhood trauma exposure. Martin-Blanco and collaborators [30] have investigated the contribution of genetic variants within genes in the HPA axis, also in the context of childhood trauma exposures, in a sample of BPD patients and controls. The authors performed a case-control study focusing on 47 SNPs in 10 HPA axis genes. Data showed an association between polymorphic variants within the FK506 Binding Protein 5 (FKBP5) and Corticotropin Releasing Hormone Receptor (CRHR) genes with the diagnosis of BPD. In particular, two FKBP5 polymorphisms, rs4713902 and rs9470079, showed significant association with BPD. Stronger associations were found in patients exposed to childhood trauma where the risk alleles of other two FKBP5 polymorphisms, rs3798347-T and rs10947563-A, were more frequently represented in patients with a history of childhood physical abuse and emotional neglect than in patients who had never experienced these trauma and controls.

All these findings suggest an association between a deregulated functionality of the HPA axis and childhood trauma and highlight the involvement of this biological system in the development of BPD.

BPD and neurotransmission

In addition to the presence of HPA axis dysfunction, several studies have also proposed that childhood trauma can affect glutamatergic, serotonergic, dopaminergic and noradrenergic transmission, suggesting that BPD is the result of alterations in several interacting neurotransmitter systems [31, 32].

Glutamatergic and N-methyl-D-aspartate (NMDA) neurotransmissions play a critical role in neurodevelopment, synaptic plasticity, learning and memory [33, 34] and alterations in all these processes have been involved also in the vulnerability and pathophysiology of BPD [35]. For example, neuroimaging studies in BPD patients as compared to controls have consistently demonstrated the presence of decreased synaptic density and volume in several brain regions involved in spatial or autobiographical memory and in the modulation of vigilance and negative emotional states, such as hippocampus and amygdala, which are also enriched in NMDA receptors [36] (see also paragraph “BPD and neuroimaging studies”). Moreover, early chronic stress and mistreatments experienced during life by BPD patients have been found able to impact dendritic arborization, thus contributing to the development of morphological alterations associated with BPD symptoms [37, 38].

The serotonin transporter gene (5-HTTLPR) and its related signaling in neurotransmission represent another system involved in the pathogenesis of BPD [39–42]. In particular, a functional single nucleotide polymorphism (SNP) within this gene (the 5-HTTLPR S/L SNP) has been widely reported to be a modulator of early life stressful events by several studies [43–45]; interestingly, it has been also associated with BPD symptoms [42, 46]. For example, Wagner and collaborators [42] investigated the effects of 5-HTTLPR S/L SNP and of early life stressful events on impulsivity, assessed by the Barratt Impulsiveness Scale (BIS), in BPD patients. The authors reported an association between the presence of stressful events with lower BIS impulsivity scores, suggesting that subjects who have experienced trauma, in particular sexual abuse, may show a reduced impulsivity as a consequence of the activation of coping mechanisms that

control behavior and social interaction. Further analyses conducted by the same authors indicated that S-allele carriers showed higher impulsivity scores when exposed to early life stressful events as compared to LL omozygotes, suggesting that patients with 5-HTTLPR S-allele are more vulnerable to early life stress. These data highlight the contribution of the serotonergic system on impulsivity in BPD [42].

Another gene suggested to be a genetic risk factor for BPD is represented by Catechol-O-methyltransferase (COMT), an enzyme catalyzing the degradation of catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine; however, literature data on the role of this gene are contrasting. In a first study conducted by Wagner and collaborators [47], the COMT Val^{158}Met SNP has been found associated with early life stressful events and impulsive aggression, assessed by the Buss-Durkee-Hostility Inventory (BDHI) sum score, in female BPD patients. In particular, the authors identified that in COMT Val^{158}Val carriers, but not in Val/Met and Met/Met carriers, childhood sexual abuse and the cumulative number of stressful events were associated with lower BDHI impulsive aggression scores. However, in another study conducted by the same authors, the effect of the COMT Val^{158}Met SNP on the association between stressful life events and impulsivity was not confirmed [48], probably due to the small sample size. The same authors [49] also investigated, in a group of BPD patients and controls, the role of (i) the COMT Val^{158}Met SNP, (ii) the 5-HTTLPR S/L variant and (iii) their interaction as genetic vulnerability factors for BPD. Data showed that the genotype COMT Met^{158}Met was over-represented in BPD patients than in controls, whereas no differences in 5-HTTLPR genotype between BPD and controls were reported. In addition, the COMT Met^{158}Met genotype was significantly over-represented in BPD patients carrying at least one 5-HTTLPR S-allele and, interestingly, an interaction between the COMT Met^{158} and the 5-HTTLPR S-allele was also observed. These results suggest an interactive effect of COMT and 5-HTTLPR gene variants on the vulnerability to develop BPD and, according to the authors, highlight again the key role of the serotonergic and dopaminergic system in the pathogenesis of BPD.

Martin-Blanco and collaborators [50] investigated the possible involvement of the noradrenergic system in BDP pathogenesis, by evaluating genetic variants within 4 noradrenergic genes. In addition to COMT, the authors selected Dopamine Beta-Hydroxylase (DBH), that acts transforming dopamine into noradrenaline, Solute Carrier Family 6 Member 2 (SLC6A2), a transporter responsible for the reuptake of extracellular neurotransmitters, and Adrenoceptor Beta 2 (ADRB2), that mediates the catecholamine-induced activation of adenylate cyclase through the action of G proteins. The authors' findings indicated that only genetic variants within 3 genes (COMT, DBH and SLC6A2) were associated with an enhanced risk to develop BPD.

These studies, taken together, show that alterations in several neurotransmitter systems could be involved in BPD pathogenesis; however, due to the small number of available studies, further investigations are needed.

BPD and the endogenous opioid system

According to Bandelow and Schmahl's theory, a reduction in the sensitivity of the opioid receptors or in the availability of endogenous opioids might constitute part of the underlying pathophysiology of BPD [51].

Endogenous opioids mainly include three classes (endorphins, enkephalins and dynorphins), which activate three types of G protein-coupled receptors (μ, δ, and κ opioid receptors [52]). One of the most important endogenous opioid is β-endorphin which is synthesized in part in the arcuate nucleus of the hypothalamus and is released into the blood, the spinal cord and in various brain regions, including reward-related areas [53]. β-endorphin is activated by a variety of stressors [54] and induce euphoria and analgesic effects (for example during childbirth and during positive experiences [55]).

The μ-opioid receptors appear to be more relevant for the social and affective regulation associated with BPD, suggesting that this system can contribute to the interpersonal vulnerabilities and intrapersonal pain of BPD. These receptors are widely distributed throughout the human Central Nervous System (CNS), with a particular density in the basal ganglia, cortical structures, thalamic nuclei, spinal cord, and specific nuclei in the brainstem [56].

The endogenous opioid system modulates responses to acute and chronic stressful and noxious stimuli that induce physical, emotional, or social pain. In animal models, the endogenous opioid system has been implicated in affiliative responses, emotion and stress regulation, including stress-induced analgesia and impulsive-like behavior [57]. Using the mother-infant separation paradigm in rhesus monkeys, Kalin and collaborators [57] studied for the first time the role of the opioid system in modulating the behavioural and neuroendocrine consequences of a brief occurring stressor. The authors conducted several experiments where animals received morphine, an opioid agonist, naloxone, an opioid antagonist or both to test the increase in vocalization and the activation of the HPA axis in infant primates separated or not from their mothers. The results showed that morphine significantly decreased separation-induced vocalizations and locomotion without affecting activity levels, whereas naloxone increased separation-induced vocalizations and environmental exploration. When the two drugs were co-administered,

the effect of morphine was reversed only with the 0.1 mg/kg dose of naloxone. The authors also assessed the effects of separation on neuroendocrine function and tested whether activation of the opioid system may attenuate these effects by measuring plasma concentrations of ACTH and cortisol in infant rhesus monkeys separated or not separated from their mothers, treated with morphine or naloxone or co-treated with the two drugs. Plasma ACTH and cortisol levels were higher in infant rhesus monkeys separated from their mothers compared to not separated ones, confirming the involvement of the HPA axis during stress exposure. However, only ACTH plasma levels were modulated by morphine and by naloxone and by their interaction in the group of infant separated by their mothers. These findings suggest that the endogenous opioid system is involved in mediating separation-induced vocalizations and influences the HPA axis activation following a stress condition.

In humans, regional endogenous opioid system activation has been associated with suppression of both sensory and affective qualities of stressors and with trait impulsivity [58–60] whereas its regional deactivation has been related to hyperalgesic responses and increases in negative affect during stress [61]. The hypothesis is that the activation of the μ-opioid receptors could have a suppressive effect during emotional or physical challenges that threaten organism homeostasis.

Research has described regional alterations in the function of the endogenous opioid system and μ-opioid receptors in brain regions involved in emotion and stress processing, decision making, and pain and neuroendocrine regulation. However, to date, there is only limited evidence of alterations of endogenous opioid levels in BPD patients. In an interesting study Prossin and collaborators [61] investigated the role of the endogenous opioid system and μ-opioid receptors in emotion regulation in un-medicated female BPD patients compared to female controls by using positron emission tomography (PET) (see paragraph "BPD and neuroimaging studies" for details).

Comparing BPD patients to their matched controls, the authors found significant differences in baseline regional μ-opioid receptor concentrations in vivo, as well as in this neurotransmitter system's response to a negative emotional challenge that can be related to some of the clinical characteristics of BPD.

BPD and neuroimaging studies

Volumetric alterations in brain areas involved in stress response

To date, several functional and structural in vivo neuroimaging studies have been performed in BPD patients, detecting alterations mainly localized in the limbic circuit and in frontal cortex. These regions are related to the distinctive clinical features of the disorder (i.e impulsivity, aggression, and emotional reactivity). The most replicated result, confirmed in recent meta-analyses [37, 62, 63], is represented by the reduction in the volumes of the hippocampus and the amygdala of BPD patients compared to controls [36, 64–69]. The robustness of this finding seems to suggest that volumetric decreases in these two brain areas could be specific for BPD and thus useful as possible endophenotypes of illness. In 2000 Driessen and collaborators [36] performed the first magnetic resonance imaging volumetric measurement of the hippocampus, amygdala, temporal lobes, and prosencephalon in 21 female BPD patients and female controls, reporting in BPD patients a volume reduction of the 16% in the hippocampus and of the 8% in the amygdala. Moreover, hippocampal volumes were negatively correlated with the extent and the duration of self-reported early trauma, but only in the entire sample of BPD patients and controls.

The role of PTSD and trauma as comorbidity with BPD on hippocampus and amygdala volumes has been object of investigation but the results are still controversial. Schmahl and colleagues [38] compared two groups of unmedicated BPD female patients with and without comorbid PTSD and 25 female controls. They found reduced hippocampal volumes only in patients with BPD and comorbid PTSD but not in BPD patients without a history of PTSD as compared to controls. Similarly, Kreisel and collaborators [70] investigated in details the hippocampal structural volumes comparing 39 BPD patients with 39 matched controls, and, although no volume differences were found between the two groups, patients with a lifetime history of PTSD had a smaller hippocampal volume (−10,5%) than those without comorbid PTSD. Boen and collaborators [71] investigated the volumes of the Cornu Ammonis (CA) and the Dentate Gyrus (DG), two hippocampal structures prone to morphological changes [72] in response to adverse environmental changes in a group of 18 women with BPD and 21 controls. The authors found that the stress-vulnerable DG-CA4 and CA2–3 subfields were significantly smaller in patients with BPD than in controls. However, they did not identify any significant association between subfield volumes and reported childhood trauma.

In another interesting study, Kuhlmann and collaborators [73] investigated alterations in the grey matter of central stress-regulating structures, including hippocampus, amygdala, anterior cingulate cortex and hypothalamus, in female patients with BPD and controls. The authors also explored whether grey matter volume of these four brain structures was associated with childhood trauma, reporting that patients with BPD showed lower hippocampal volumes than healthy controls, but higher volumes in the hypothalamus. Interestingly,

hypothalamic volume correlated positively with a history of trauma in patients with BPD.

Two recent meta-analyses [37, 63] evaluated whether the magnitude of hippocampus and amygdala volume reductions may be associated with state-of-illness factors and psychiatric disorders (i.e. PTSD) which often co-occured with BPD. In the Rodrigues' meta-analysis, the authors included 7 articles with a total number of 124 patients and 147 controls. They showed that both the left and the right sides of hippocampal volumes were reduced in BPD patients with PTSD when compared to controls. The left hippocampal volume was not significantly smaller in BPD patients without PTSD relative to healthy controls and the right hippocampal volume was reduced in patients with BPD without comorbid PTSD, but to a lesser degree than in BPD patients with PTSD. In contrast, the results reported by Ruocco's meta-analysis [37] which included 11 studies with a total number of 205 BPD patients and 222 controls, revealed that bilateral volume reductions of the amygdala and hippocampus were unrelated to comorbid Major Depressive Disorder (MDD), PTSD, or substance use disorders.

Taken together, all these studies show that the main brain regions involved in BPD are those associated to stress and highlight the importance of classifying subgroups of patients with BPD, especially taking into account the presence of comorbidity with PTSD or of a history of childhood trauma. Notwithstanding, the association between the volume reduction and the degree to which childhood trauma could be responsible for these changes remains unclear.

Endogenous opiod system alterations in brain regions involved in stress response

Despite a large amount of data referred to volumetric and morphological alterations in brain regions associated to specific clinical features of BPD, not many neuroimaging studies have been conducted to investigate the role of the endogenous opioid system in BPD. As previously mentioned, Prossin and collaborators [61] measured the in vivo availability of the μ-opioid receptors (non-displaceable binding potential (BPND)) in a group of unmedicated female BPD patients compared to female controls by using PET and the selective radiotracer [11C] carfentanil at baseline and during sustained sadness states. Patients had greater regional μ-opioid BPND than controls at baseline (neutral state) in the left nucleus accumbens, the hypothalamus, and the right hippocampus/parahippocampus relative to comparison subjects, showing an endogenous opioid system activation. As suggested by the authors, differences between BPD patients and controls in baseline in vivo μ-opioid receptor concentrations and in the endogenous opioid system response to a negative emotional challenge can be related to some of the clinical characteristics of BPD patients. These findings show alterations in the function of the endogenous opioid system and μ-opioid receptors in brain regions involved in emotion and stress processing, decision making, and pain and neuroendocrine regulation, features also associated with BPD.

BPD and epigenetic mechanisms

The influence of environmental factors, such as childhood trauma, has been suggested to occur through epigenetic mechanisms, which may underlie gene-environment associated vulnerability to develop stress-related disorders [74] including BPD where childhood trauma history occurs in most of the patients (with a range between 30 and 90%) [7, 9].

Among the most investigated epigenetic mechanisms there are: (i) DNA methylation, which occurs at CG dinucleotides (CpG) and can influence the spatial structure of the DNA and the binding or the repression of specific DNA-binding proteins to the DNA [75], (ii) histone modifications, which influence the condensation of the DNA around histone proteins and regulate the accessibility of functional regions to transcriptional factors [76] and (iii) post-transcriptional regulation by non-coding RNAs such as microRNAs (miRNAs) [77].

All these epigenetic processes and, in particular, changes in DNA methylation have been widely investigated in the context of long-term negative effects of early life stressful events. In non-human primates and in rodents, several paradigms of stress early in life, including maternal separation or prenatal stress have been associated with epigenetic alterations via DNA methylation [78, 79]. For example, non-stressed dams during pregnancy showed increased frequency of licking and grooming in the first week of the puppies' life that were associated with changes in DNA methylation within the promoter of genes, such as glucocorticoid receptor gene (NR3C1), known to be involved in behavior and neurodevelopment.

The hypothesis is that the quality of maternal care, affected by stress or depression in pregnancy and postpartum [80, 81] could impact, through epigenetic mechanisms, on gene expression and behavioral traits that are maintained throughout life [78].

Recently, McGowan and colleagues [79] examined DNA methylation, histone acetylation and gene expression in a 7 million base pair region of chromosome 18 containing the NR3C1 gene in the hippocampus of adult rat offspring, whose mothers differed in the frequency of maternal care. The authors found that the adult offspring of high compared to low maternal care showed a pattern of regions spanning the NR3C1 gene which were differentially methylated and acetylated, highlighting the idea that epigenetic changes, in the context of early life

stress, involve alterations in gene-networks rather than in a single or few genes.

Similarly, studies in humans reported similar results as those found in rodents, including the increased methylation levels within the NR3C1 promoter region in subjects who reported a history of early life adverse events [82–84]. For example, in another interesting study, McGowan and collaborators [82] found that in humans the cytosine methylation levels of the NR3C1 promoter were significantly increased in the postmortem hippocampus obtained from suicide victims with a history of childhood abuse as compared with those from suicide victims with no childhood abuse or with control samples. Decreased levels of NR3C1 mRNA were also identified, suggesting an effect of childhood abuse on NR3C1 methylation status and gene expression, independently from suicide.

Several epigenetic studies have been also conducted in control subjects characterized for a history of childhood trauma compared to those with no childhood trauma. In this context, Suderman and colleagues [85] have demonstrated, by using a genome-wide promoter DNA methylation approach, an abuse-associated hypermethylation in 31 miRNAs in a sample of control adult males exposed to childhood abuse. The hypermethylated state for 6 of these miRNAs was consistent with an hypomethylation status of their target genes.

Reduced methylation levels of FKBP5 gene within regions containing functional glucocorticoid responsive elements (GRE) were also found in the blood of control individuals exposed to childhood abuse when compared to subjects without a history of trauma [86]. This demethylation was linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global effect on the function of immune cells and brain areas associated with stress regulation. Thus, according to the authors, the changes in FKBP5 methylation levels might increase the differential responsiveness of FKBP5 to GR activation that can remain stable over time. Moreover, Labontè and colleagues [87] have conducted a genome-wide study of promoter methylation in the hippocampus of individuals with a history of severe childhood abuse and control subjects. Methylation profiles were then compared with corresponding genome-wide gene expression profiles. Among all the differentially methylated promoters, 248 showed hypermethylation whereas 114 demonstrated hypomethylation and genes involved in cellular/neuronal plasticity were among the most significantly differentially methylated.

Despite the contribution of DNA methylation has been extensively investigated in association with childhood trauma in the context of pathologies related to stress, studies on the possible involvement of epigenetic mechanisms in BPD vulnerability are only at their birth. Indeed, only few studies are available. In particular, Martin-Blanco and colleagues, investigated the association between NR3C1 methylation status, history of childhood trauma and clinical severity in blood samples of BPD subjects, showing an association between NR3C1 methylation and childhood trauma, in the form of physical abuse, and a trend towards significance for emotional neglect [88]. Regarding NR3C1 methylation and clinical severity, the authors also found a significant association with self injurious behavior and previous hospitalizations. All these findings support the hypothesis that alterations in NR3C1 methylation can occur early in life as consequence of stress exposure and can persist up to adulthood where subjects with higher NR3C1 methylation levels are also those with enhanced vulnerability to develop BPD.

Above to DNA methylation changes within NR3C1, hypo- or hyper-methylation within other genes have been found to play a key role in mediating the impact of early life stress on the development of stress-related disorders, including BPD [89–92]. For example, in a study conducted by Dammann and colleagues [89] DNA methylation pattern of 14 genes, selected because previously associated with BPD and other psychiatric disorders, (COMT, Dopamine Transporter 1 (DAT1), Gamma-Aminobutyric Acid Type A Receptor Alpha1 Subunit (GABRA1), G Protein Subunit Beta 3 (GNB3), Glutamate Ionotropic Receptor NMDA Type Subunit 2B (GRIN2B), 5-Hydroxytryptamine Receptor 1B (HTR1B), 5-Hydroxytryptamine Receptor 2A (HTR2A), Serotonin Transporter 1 (5-HTT), Monoamine Oxidase A (MAOA), Monoamine Oxidase B (MAOB), Nitric Oxide Synthase 1 (NOS1), NR3C1, Tryptophan Hydroxylase 1 (TPH1) and Tyrosine Hydroxylase (TH)), was analyzed in the whole blood of BPD patients and controls. An increase in the methylation levels of HTR2A, NR3C1, MAOA, MAOB and COMT was observed in BPD patients as compared to controls, suggesting that an increased methylation of CpG sites within these genes may contribute to BPD aetiopathogenesis. Recently, Perroud and colleagues [91] investigated the role of childhood trauma on the methylation status of the Serotonin 3A Receptor (5-HT_{3A}R), including several CpGs located within or upstream this gene. They analyzed its association with clinical severity outcomes, also in relation with a functional genetic SNP (rs1062613) within 5-HT_{3A}R in adult patients with Bipolar Disorder, BPD, and Attention Deficit Hyperactivity Disorder (ADHD). The results showed that differential 5-HT_{3A}R methylation status was dependent on the history of childhood maltreatment and the clinical severity of the psychiatric disorder; this association was not specifically restricted to one specific psychiatric disorders

investigated by the authors, but was found in patients who reported the higher severity indexes of childhood maltreatment, mainly represented by BPD patients. In particular, childhood physical abuse was associated with higher 5-HT_{3A}R methylation levels, whereas childhood emotional neglect was inversely correlated with CpG1 I methylation levels. As suggested by the authors, these results highlight the need to search for history of childhood maltreatment in patients suffering from psychiatric disorders as these events could be associated with the worse negative outcomes. Moreover, the authors found a modulation of the $5HT_{3A}$R methylation status by rs1062613 at CpG2 III, where patients carrying the risk CC genotype showed the highest levels of methylation at CpG2 III. Since C allele has been also associated with a lower expression levels of $5HT_{3A}$R, the authors suggested that increased methylation, due to exposure to childhood maltreatment, could lead to a further decrease in the expression of $5HT_{3A}$R mRNA.

Aiming to identify novel genes that may exhibit aberrant DNA methylation frequencies in BPD patients, Teschler and collaborators [93] performed a genome-wide methylation analysis in the blood of BPD female patients and female controls. The authors reported increased methylation levels of several genes, including neuronal adaptor proteins (Amyloid Beta Precursor Protein Binding Family A Member 2 (APBA2) and Amyloid Beta Precursor Protein Binding Family A Member 3 (APBA3)), zinc-finger transcription factors (GATA Binding Protein 4 (GATA4)), voltage-gated potassium channel gene (Potassium Voltage-Gated Channel Subfamily Q Member 1 (KCNQ1)), guanine nucleotide exchange factors (Proto-Oncogene MCF-2 (MCF2)), adhesion molecules (Ninjurin 2 (NINJ2)) and G protein-coupled receptors (Trace Amine Associated Receptor 5 (TAAR5)) in BPD samples compared to controls. Similarly, using a whole-genome methylation approach, Prados and colleagues [94] analyzed the global DNA methylation status in the peripheral blood leukocytes of BPD patients with a history of childhood adversity and also in patients with MDD characterized by a low rate of childhood maltreatment. Contrary to Teschler [93], who used control subjects as reference group, in this study the authors used MDD subjects, most of them suicide attempters, thus controlling not only for MDD but also for a history of suicide. The authors also assessed possible correlations between methylation signatures and the severity of childhood maltreatment. Data showed that several CpGs within or near genes involved in inflammatory processes (Interleukin 17 Receptor A (IL17RA)), regulation of gene expression (miR124–3) and neuronal excitability and development/maintenance of the nervous system (Potassium Voltage-Gated Channel Subfamily Q Member 2 (KCNQ2)) were differentially methylated, either in BPD compared with MDD or in relation to the severity of childhood maltreatment.

In a more recent study, Teschler and collaborators [95] have analyzed also DNA methylation patterns of the ribosomal RNA gene (rDNA promoter region and 5′-external transcribed spacer/5′ETS) and the promoter of the proline rich membrane anchor 1 gene (PRIMA1) in peripheral blood samples of female BPD patients and controls. The authors have identified a significant aberrant methylation of rDNA and PRIMA1 in the group of BPD patients. Specifically, the average methylation of 6 CpG sites in the promoter of PRIMA1 was 1.6-fold higher in BPD patients compared to controls. In contrast, the methylation levels of the rDNA promoter region and the 5′ETS were significantly lower (0.9-fold) in patients with BPD compared to controls. Furthermore, decreased methylation levels were found for nine CpGs located in the rDNA promoter region and for 4 CpGs at the 5′ETS in peripheral blood of patients compared to controls. These results suggest that aberrant methylation of rDNA and PRIMA1 could be associated with the pathogenesis of BPD.

Taken together, all these studies reveal a complex interplay between BPD, early-life stressful adversities and epigenetic signatures.

BPD and neuroplasticity (the role of BDNF)

Neuroplasticity refers to brain-related mechanisms associated with the ability of the brain to perceive, adapt and respond to a variety of internal and external stimuli [96, 97], including stress.

The exposure to acute stressful challenges can induce several beneficial and protective effects for the body, which responds to almost any sudden, unexpected events by releasing chemical mediators – i.e. catecholamines that increase heart rate and blood pressure – and help the individual to cope with the situation [20, 98–101]. However, a chronic exposure to stress and thus a chronic exposure to glucocorticoids can have negative and persistent effects on the body, including altered metabolism, altered immunity, enhanced inflammation, cognitive deficits, and also an enhanced vulnerability for psychiatric disorders and for medical conditions such as cardiovascular disease, metabolic disorders and cancer [102, 103].

Neurotrophic factors, and in particular the neurotrophin Brain-Derived Neurotrophic Factor (BDNF), have been identified as key mediators of stress on neuronal connectivity, dendritic arborization, synaptic plasticity and neurogenesis [104–107]. Since its crucial role in brain development and brain plasticity, BDNF has been widely investigated also in several psychiatric diseases, including BPD [108].

For example, Koenigsberg and colleagues [109] found a decrease of Protein Kinase C (PKC) isoenzyme, which

is a molecule downstream the activation of BDNF, and BDNF protein levels in the blood of BPD patients, suggesting an alteration of BDNF signaling and consequently of neuroplasticity-related mechanisms in BPD. In another study, Tadic and collaborators [49] investigated the association between BPD and genetic variants within HTR1B and BDNF genes. Although data showed no significant differences in genotype or haplotype distribution for both HTR1B and BDNF variants between BPD patients and controls, logistic regression analyses revealed an association between the HTR1B A-161 variant and the functional BDNF 196A allele in BPD.

Importantly, several findings have also documented epigenetic modifications on BDNF gene in patients with BPD, suggesting that childhood maltreatment in BPD patients can cause long term epigenetic alterations of genes crucially involved in brain functions and neurodevelopment, including BDNF, and that these alterations may contribute to enhanced vulnerability to develop BPD pathology. In this regard, Perroud and collaborators [90] measured the percentage of methylation at BDNF CpG exons I and IV and also plasma BDNF protein levels in subjects with BPD and controls. The authors reported significantly higher methylation status in both CpG regions in patients than in controls, with the number of childhood trauma exposures associated with the high levels of BDNF methylation. Moreover, BPD patients had significantly higher BDNF plasma protein levels than controls, but this increase was not associated with changes in BDNF methylation status. More recently, Thaler and collaborators [92] analyzed DNA methylation patterns in the promoter region of BDNF gene in women with bulimia nervosa and with history of BPD and/or trauma events. They reported that bulimia nervosa was associated per se with an hypermethylation within BDNF promoter region sites. This was particularly evident when co-occurring with childhood abuse or BPD.

Overall, these studies support the hypothesis that childhood trauma could be associated with changes in BDNF epigenetic signature, that in turn could contribute to alter cognitive functions in BPD patients. Indeed, higher levels of gene methylation are commonly accompanied by a reduced gene expression. Thus higher BDNF methylation levels should determine reduced expression of BDNF gene and reduced BDNF mRNA levels are widely observed in patients with psychiatric diseases [110–112].

Conclusions

Up to now, neither a specific gene variant or biological mechanism has been exclusively associated with BPD, but the onset of this disorder has been suggested to depend on the combination of a vulnerable genetic background with adverse environmental factors during childhood.

Among the biological systems found involved in BPD pathogenesis and particularly affected by childhood trauma events, there are: the HPA axis, the neurotransmission mechanisms, the endogenous opioid system and the neuroplasticity. In line with the involvement of these processes, neuroimaging studies in BPD patients have shown volume reductions in the hippocampus and amygdala, both brain regions mainly involved in stress responses, cognition, memory and emotion regulation and an increase in the μ-opioid receptors in the same areas.

Among the environmental factors, early life stressful events, in particular childhood trauma, have been proposed to negatively impact brain development through epigenetic mechanisms. Although a complex interplay between BPD, early-life stressful adversities and epigenetic signatures has been suggested, further investigations are needed in order to better understand the role of genetic background and traumatic events during childhood in the onset of BPD. A better comprehension of these interactions could allow to identify at risk subjects, who could be treated with preventive therapies, such as psychotherapy, and to prevent or minimize the development of the disease later in life.

Abbreviations

5-HT_{3A}R: Serotonin 3A Receptor; 5-HTT: Serotonin Transporter 1; 5-HTTLPR: Serotonin transporter gene; ACTH: Adrenocorticotropic Hormone; ADHD: Attention Deficit Hyperactivity Disorder; ADRB2: Adrenoceptor Beta 2; APBA2: Amyloid Beta Precursor Protein Binding Family A Member 2; APBA3: Amyloid Beta Precursor Protein Binding Family A Member 3; AVP: Arginine Vasopressin; BDHI: Buss-Durkee-Hostility Inventory; BDNF: Brain-Derived Neurotrophic Factor; BIS: Barratt Impulsiveness Scale; BPD: Borderline Personality Disorder; CA: Cornu Ammonis; CNS: Central Nervous System; COMT: Catechol-O-methyltransferase; CpG: CG dinucleotides; cPTSD: complex Post-Traumatic Stress Disorder; CRF: Corticotropin-Releasing Factor; CRHR: Corticotropin Releasing Hormone Receptor; DAT1: Dopamine Transporter 1; DBH: Dopamine Beta-Hydroxylase; DESNOS: Disorders of Extreme Stress Not Otherwise Specified; DEX: Dexamethasone; DG: Dentate Gyrus; FKBP5: FK506 Binding Protein 5; GABRA1: Gamma-Aminobutyric Acid Type A Receptor Alpha1 Subunit; GATA4: GATA Binding Protein 4; GNB3: G Protein Subunit Beta 3; GR: Glucocorticoid Receptor; GRE: Glucocorticoid Responsive Elements; GRIN2B: Glutamate Ionotropic Receptor NMDA Type Subunit 2B; HPA axis: Hypothalamic-Pituitary-Adrenal axis; HTR1B: 5-Hydroxytryptamine Receptor 1B; HTR2A: 5-Hydroxytryptamine Receptor 2A; IL17RA: Interleukin 17 Receptor A; KCNQ1: Potassium Voltage-Gated Channel Subfamily Q Member 1; KCNQ2: Potassium Voltage-Gated Channel Subfamily Q Member 2; MAOA: Monoamine Oxidase A; MAOB: Monoamine Oxidase B; MCF2: Proto-Oncogene MCF-2; MDD: Major Depressive Disorder; miRNAs: microRNAs; MR: Mineralcorticoid Receptor; NINJ2: Ninjurin 2; NMDA: N-methyl-D-aspartate; NOS1: Nitric Oxide Synthase 1; NR3C1: Glucocorticoid receptor gene; PET: Positron Emission Tomography; PKC: Protein Kinase C; PRIMA1: Prolin Rich Membrane Anchor 1; PTSD: Post-Traumatic Stress Disorder; PVN: Paraventricular Nucleus; SLC6A2: Solute Carrier Family 6 Member 2; SNP: Single nucleotide polymorphism; TAAR5: Trace Amine Associated Receptor 5; TH: Tyrosine Hydroxylase; TPH1: Tryptophan Hydroxylase 1

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Authors' contributions
N.C. managed the literature searches and wrote the first draft of the manuscript. R.R. and M.L. managed the literature searches and completed the manuscript. A.C. revised and approved the final version of the manuscript. All authors gave their scientific contribution and have approved the final manuscript.

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Author details
[1]Biological Psychiatry Unit, IRCCS Istituto Centro San Giovanni di Dio - Fatebenefratelli, via Pilastroni 4, Brescia, Italy. [2]Psychiatry Unit, IRCCS Istituto Centro San Giovanni di Dio - Fatebenefratelli, via Pilastroni 4, Brescia, Italy. [3]Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College London, 125 Coldharbour Lane, London SE5 9NU, UK. [4]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 125 Coldharbour Lane, London SE5 9NU, UK.

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