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No. 51736-1-II

IN THE COURT OF APPEALS
FOR THE STATE OF WASHINGTON
DIVISION TWO

In re Personal Restraint Petition of

JAMES CHARLES MATHES,

Petitioner

Kitsap County Superior Court No. 14-1-00301-1

REPLY BRIEF OF PETITIONER

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I. INTRODUCTION

Mr. Mathes hereby submits this Reply to correct the State's many mischaracterizations, misrepresentations, and misstatements and assert that his petition warrants not only resentencing, but also new trial due to the multiple instances of ineffective assistance of counsel. The State's concession of error as to the offender score issue is well-received.

The record, first, is clear that from the very beginning of the representation all of the way through sentencing, counsel continually and consistently failed to effectively advise Mr. Mathes of the specific consequences of proceeding to trial rather than accepting a plea deal. Mr. Mathes, critically, had no idea that the *mandatory* firearm enhancements would be imposed *consecutively with no good time* and that he would have to serve all of that time prior to accruing any earned release time on the underlying offenses.

Despite Mr. Mathes's *pro se* submission, the Supplemental Brief (Supp. Br.) filed on his behalf, and Petitioner's Verification that the contents of the Supplemental Brief were true and correct and that he consented to its filing, the State argues that there is no evidence that he was unaware of the harsh implications of the firearm enhancements. Brief of Respondent (Resp.) at 23-24. To make the record unequivocal, attached hereto as Exhibit A is the Declaration of James Mathes in

Support of Petition. Attached hereto as Exhibit B is the Declaration of Craig Suffian in Support of Petition, which details that Mr. Mathes repeatedly expressed that he never knew about the mandatory, consecutive with no earned early release credits nature of the firearm enhancements, but that counsel did not have another opportunity to visit him before filing the Supplemental Brief. Counsel's declaration also explains that Dr. Barnard was not the product of "expert shopping," but rather that he was the sole qualified practitioner counsel who was available *and* who could assess Mr. Mathes on one of the very few days available for visitation.

In his own Declaration, Mr. Mathes recounts that trial counsel, Ron Ness, never advised him of the statutory maximum he might face after either a plea deal or conviction at trial. Mr. Mathes also never understood that *each* firearm enhancement would necessarily run consecutively with no good time and that he could be sentenced on multiple enhancements. While he understood that he would be able to earn 10% early release credit towards assault in the first degree and 33% early release credit towards assault in the second degree, he had no knowledge that he could be sentenced for more than one enhancement and that each would run consecutively with no good time.

Mr. Mathes further clarifies that he anticipated only three new charges—not eight; and, he never knew anything about the consecutive

nature of the attendant enhancements. Since the members of his family have relatively short life spans and tend to perish between the ages of 65 and 70, he viewed any sentence of 25 years or longer as a life sentence (he was 44 at the time of sentencing). He never had any idea that he might possibly face a sentence of 720 months; he was informed only that he might receive a very long sentence of an unspecified amount of time.

Had trial counsel properly calculated his offender score and negotiated as based upon a correct criminal history, Mr. Mathes likely would have accepted the resulting offer. Instead, due to counsel's deficient or absent advisements, Mr. Mathes proceeded to trial and is now serving what is tantamount to a life sentence.

Mr. Mathes's Declaration, furthermore, raises a new issue related to counsel's ineffective assistance in advising him to assert his Fifth Amendment and Const. art. I, §9 because of counsel's misapprehension that Mr. Mathes's criminal history would be admissible against him

Counsel's misunderstanding of these issues infected the entirely of the process—from plea negotiations through sentencing.

On the literal eve of trial, the State added eight new counts with multiple enhancements; the defense anticipated only three additional counts. Counsel should have objected or moved for continuance. At the very least, counsel should have properly advised Mr. Mathes of the

potentially dire consequences of a jury convicting him as charged on all of the counts and enhancements and a court sentencing him accordingly.

During trial, counsel capitulated to the State's motions and failed to offer seemingly meritorious arguments that Mr. Mathes's statements to law enforcement personnel and lay witnesses were admissible to demonstrate to show his state of mind, his intoxication, and his lack of intent to commit his offenses. Even if irrelevant towards a diminished capacity defense because the trial court excluded Dr. Muscatel's testimony, such statements were nevertheless admissible as non-hearsay evidence of state of mind. Given the defense of suicide by police officer, this evidence was not only relevant and admissible, but crucial and apt to have changed the result at trial.

Counsel, in like manner, inexplicably moved to suppress helpful evidence. While he was, fortunately, largely unsuccessful, as he later tried to admit such statements and cited to them in closing, this is yet another example of ineffective assistance.

The State's analysis as to Dr. Barnard's opinion, based upon records which Dr. Muscatel acknowledges he should have reviewed but which counsel failed to provide, is baseless and confusing. The issue is straightforward: whether counsel effectively prepared Dr. Muscatel. Given the wealth of records documenting Mr. Mathes's diagnosed mental

health issues since 1999 that counsel neglected to obtain and provide to Dr. Muscatel, the answer is a resounding, "No."

Dr. Muscatel's Report, a copy of which is attached hereto for the Court's convenience as Exhibit C, lists the limited sources he consulted—solely the case discovery. Dr. Barnard's report, by contrast, includes not only discovery, but also all of Mr. Mathes's mental health records dating back to 1999 complete with years of testing and diagnoses. This is not newly discovered evidence given that counsel surely could have discovered the evidence before trial, but rather an ineffective assistance claim that counsel failed to discover such relevant evidence and present it to Dr. Muscatel. The cases holding that new expert opinions based upon *the facts available to trial experts* are thus inapposite. See Resp. at 36-40.

Counsel, moreover, even after the court twice denied his attempts to proffer a diminished capacity defense and despite abundance evidence of Mr. Mathes's intoxication, never tried to offer any such evidence and never requested a voluntary intoxication instruction. Ms. Toste testified that he injected drugs the night of the incident, Roy Mathes testified that his son was gone, Ms. Vierra was aware that he had been using methamphetamine that night as well as in the recent past, Pat Dawson and Norm Reinhardt also had knowledge of his addiction, and there was a toxicology screen in discovery demonstrating that Mr. Mathes had

recently taken methamphetamine and benzodiazepine, yet counsel failed to emphasize (or move to admit) this evidence. He also never offered evidence that the effects of methamphetamine typically last from six to 12 hours and for as long as 24 hours and can result in psychosis. See Exhibit D, materials relating to methamphetamine. The State harps on the fact that there was no evidence that Mr. Mathes ingested any drugs after Ms. Toste witnessed him inject himself and that he must have been out since he asked Ms. Vierra to get more drugs. See Resp. at 41, 50-51. Testimony about the effects of methamphetamine would have bridged that gap and likely supported an instruction on voluntary intoxication. Counsel completely failed on this entire issue—from failing to introduce and elicit relevant helpful evidence to failing to request an instruction.

As to Mr. Mathes's *pro se* claims, it seems that the State acknowledges that Ms. Toste provided false or inconsistent testimony. Resp. at 55-56, 58-60. While materiality is debatable, counsel certainly should have impeached her on the basis of her inconsistencies to impugn her credibility. She willingly disobeyed a court order and misrepresented this fact to the jury. The same analysis applies to Detective Green's inconsistencies. Counsel also should have impeached Ms. Toste on grounds that she knew Mr. Mathes was high on methamphetamine and not heroin—as the toxicology screen which he neglected to admit shows.

Mr. Mathes appreciates the State's concession of error as to his offender score and is confident that the other sentencing errors will be rectified during his resentencing process, if he fails to receive the more substantial relief which he seems to warrant.

The State, finally, argues against cumulative error. Pursuant to the United States Supreme Court's constitutional jurisprudence in Strickland and in the Ninth Circuit, the prejudicial impact of claims of ineffective assistance are viewed cumulatively, not piecemeal. Here, each of the many errors, standing alone, warrants new trial. Collectively, they mandate new trial.

II. ARGUMENT

New trial is required because any one ground of ineffective assistance, standing alone, is sufficient and because all of the errors, cumulatively, mandate new trial.

While the State provided multiple pages of boilerplate law regarding the standard of review, see Resp. at 14-18, all of Mr. Mathes's claims relate to counsel's ineffective assistance. Ineffective assistance, in turn, in and of itself constitutes constitutional error such that the demonstration of prejudice required for a claim satisfies the actual and substantial prejudice on collateral relief. Matter of Harvey, 3 Wn.App.2d 204, 215, 415 P.3d 253 (2018) (citing In re Crace, 174 Wn.2d 835, 846–47, 280 P.3d 1102 (2012)).

The State, moreover, cites to case law about relitigation of issues and finality, but never makes any specific arguments or claims. Resp. at 16-17. Lacking application of law to fact, the State thus fails to raise any substantive procedural barrier to any of Mr. Mathes's claims.

A criminal defendant is entitled to effective assistance of counsel. State v. Lopez, 190 Wn.2d 104, 115, 410 P.3d 1117 (2018) (citing; Const. art. I, § 22). Effective assistance includes many things, but at the very least "the overarching duty to advocate the defendant's cause and the more particular duties to consult with the defendant on important decisions and to keep the defendant informed of important developments in the course of the prosecution." Id. at 115-116 (quoting In re Per. Restraint of Yung-Chen Tsai, 183 Wn.2d 91, 100, 351 P.3d 138 (2015) (alterations in original) (quoting Strickland v. Washington, 466 U.S. 668, 688, 104 S.Ct. 2052, 80 L.Ed.2d 674 (1984)). The right to effective assistance also includes a "reasonable investigation by defense counsel" and "expert assistance necessary to an adequate defense." Id. (citations omitted).

Here, counsel was ineffective for: (1) consistently failing to sufficiently apprise Mr. Mathes of his potential sentence—particularly the ramifications of the firearm enhancements—and proceeding to trial with no additional preparation after the State added eight new charges with enhancements; (2) engaging in plea discussions without properly

calculating Mr. Mathes's offender score and without advising him that he could be convicted of multiple mandatory, consecutive, no good time firearm enhancements; (3) failing to offer admissible, helpful mental state evidence; (4) moving to suppress helpful evidence he later (mostly) unsuccessfully tried to admit and cited in closing; (5) failing to prepare Dr. Muscatel with evidence of Mr. Mathes's longstanding documented mental health issues; (6) failing to admit evidence of intoxication and the effects of methamphetamine and failing to request a voluntary intoxication instruction; (7) failing to impeach Ms. Toste and Det. Green with their inconsistent statements and failure to impeach Ms. Toste's representation that she believed Mr. Mathes was high on heroin; and (8) improperly advising that if Mr. Mathes testified, all of his criminal history would be admissible.

Viewed individually or collectively, these errors warrant relief.

A. COUNSEL FAILED TO MOVE FOR CONTINUANCE OR DISMISSAL WHEN PRESENTED WITH EIGHT NEW CHARGES WITH ENHANCEMENTS ON THE EVE OF TRIAL

As counsel failed to request a continuance or move for dismissal when the state filed its First Amended Information, which added eight counts—nearly all with some sort of enhancement—on the day of trial call and just seven days before the state's opening, such deficient performance

forced Mr. Mathes to choose between effective counsel and his speedy trial rights. New trial is thus warranted.

Although Mr. Mathes was, indeed, aware of the State's intention to add charges, he believed that there would be three—not eight—new charges, and he and counsel never discussed the new developments. This failure violated counsel's duties of loyalty, communication, and consultation to Mr. Mathes's serious prejudice.

Even if counsel was sufficiently familiar with facts of the case that he anticipated the eight new charges with enhancements, there is little chance that he could have been prepared to proceed to trial in such little time. And, as Mr. Mathes's Declaration attests, counsel never discussed with him the gravity of the new charges and enhancements.

The State contends that the lack of an objection distinguishes this case from State v. Michielli, 132 Wn.2d 229, 937 P.2d 587 (1997). Resp. at 19. This, however, is the precise issue—that counsel's failure to object and preserve—lest prevail on—this issue constitutes ineffective assistance. The State's arbitrary piling on of nearly three times the amount of charges it represented it might file (eight rather than three), nearly all with sentencing enhancements, without justification on the eve of trial is the misconduct/ mismanagement. The prejudice is the fact that Mr. Mathes went to trial without knowing the consequences of his choice and with an

unprepared attorney who was suffering from serious medical concerns. He, essentially, sacrificed his right to speedy trial in favor of trial with an ineffective attorney.

While State v. Brooks pertained to discovery violations, the maxim that the State "cannot by its own unexcused conduct force a defendant to choose between his speedy trial rights and his right to effective counsel" applies equally to untimely and excessive amendment of an information. 149 Wn.App. 373, 387, 203 P.3d 397 (2009). Relief is thus warranted.

B. COUNSEL FAILED TO PROPERLY ADVISE MR. MATHES DURING PLEA NEGOTIATIONS

As counsel offered advice based upon an incorrect offender score, failed to apprise Mr. Mathes of the potential sentencing exposure he faced if he proceeded to trial, and never made clear that each of the enhancements would run consecutively with no good time and be served prior to the underlying offenses, new trial is required.

1. Offender Score

Without ever properly calculating Mr. Mathes's offender score, counsel engaged in plea negotiations, tried the case, and then rapidly dispensed with sentencing. This was ineffective assistance.

While the State's concession of error is welcome, the error was not limited to just sentencing, but rather pervaded the entirely of the

proceedings. The parties, though, seem to agree that this was sentencing ineffective assistance. See, e.g. State v. Davis, 3 Wn.App.2d 763, 418 P.3d 199 (2018) (counsel's failure to object to a wrong offender score is ineffective assistance of counsel and prejudice "is self-evident as it increases the defendant's offender score"); In re Pers. Restraint Petition of Crawford, 150 Wn.App. 787, 209 P.3d 507 (2009).

In the plea context, "counsel must reasonably investigate and assess the potential consequences and sentencing ramifications to ensure that a defendant makes an informed decision whether to accept or reject a plea offer." Crawford v. Fleming, 323 F. Supp. 3d 1186, 1192–93 (D. Or. 2018), appeal dismissed sub nom. Crawford v. Rosenblum, No. 18-35505, 2018 WL 4348178 (9th Cir. Sept. 5, 2018) (citing United States v. Day, 969 F.2d 39, 43 (3d Cir. 1992) ("Knowledge of the comparative sentencing exposure between standing trial and accepting a plea offer will often be crucial to the decision whether to plead guilty."); Iaea v. Sunn, 800 F.2d 861, 865 (9th Cir. 1986) ("Because an intelligent assessment of the relative advantages of pleading guilty is frequently impossible without the assistance of an attorney, counsel have a duty to supply criminal defendants with necessary and accurate information.").

It thus follows that where counsel "fails to reasonably investigate or seek critical sentencing information and provides inaccurate or

misleading advice as a result … performance is deficient." Id. at 1193 (citing, e.g., United States v. Gordon, 156 F.3d 376, 380 (2d Cir. 1998) (faulty advice during the plea process about potential sentencing exposure is ineffective assistance); see also State v. Estes, 188 Wn.2d 450, 463–64, 395 P.3d 1045, 1052 (2017) ("Even if the trial itself is free from constitutional flaw, the defendant who goes to trial instead of taking a more favorable plea may be prejudiced from either a conviction on more serious counts or the imposition of a more severe sentence.") (quoting Lafler v. Cooper, 566 U.S. 156, 166, 132 S.Ct. 1376, 182 L.Ed.2d 398 (2012)); Riggs v. Fairman, 178 F. Supp. 2d 1141, 1147 (C.D. Cal. 2001), aff'd, 399 F.3d 1179 (9th Cir. 2005) (counsel's failure to review Petitioner's rap sheet, failure to ask specific questions concerning Petitioner's prior robbery case, and failure otherwise to investigate the prior case was ineffective assistance of counsel).

Even if there is any "uncertainty about the outcome of plea bargain negotiations" reversal is still required "where confidence in the outcome is undermined." Estes, 188 Wn.2d at 464. Such is the case here.

2. Firearm Enhancements

Given that (1) the State's argument is solely factual, see Resp. at 22-25, and (2) Mr. Mathes's Declaration, see Ex. A (in addition to his *pro se* pleading, the Supplemental Brief, and Petitioner's Verification),

definitively provides the purportedly lacking evidence of counsel's faulty advisements, there is scant question that relief is required on this basis.

The State claims that Mr. Mathes should have known about the specific details of the firearm enhancements because of the advisements on the charging documents. Resp. at 24. The charging documents, however, say *nothing* about the *nature* of the enhancements—that they are automatically imposed consecutively to each other, must be served before the underlying offenses, and are not subject to earned early release credits.

Due to his past experiences with the criminal justice system, Mr. Mathes was familiar with the concept of good time. He knew the difference between 10% good time for first degree assault and 33% good time for second degree assault. He never imagined, though, that he could be sentenced to more time in enhancements, alone, than was offered in the plea deals. See Ex. A. As previously briefed, Estes, supra, and In re McCready, 100 Wn.App. 259, 996 P.2d 658 (2000), seem dispositive in mandating new trial due to counsel's deficient advice concerning the firearm enhancements.

C. COUNSEL FAILED TO ADMIT SIGNIFICANT HELPFUL EVIDENCE DUE TO HIS LACK OF KNOWLEDGE OF THE APPLICABLE LAW

Rather than attempt to proffer a voluntary intoxication defense or offer evidence of Mr. Mathes's drug use and bizarre behavior leading up

to his criminal charges to argue against intent, counsel capitulated because he did not know the controlling law. This was ineffective assistance.

First, *all* of Mr. Mathes's statements at the crime scene and when he awoke from unconsciousness in the hospital were admissible as present sense impressions, excited utterances, or statements relating to his state of mind. See ER 803(a)(1)-(3); Resp. at 31.

With respect to the historical information, the State acknowledges that "evidence of prior mental states may be probative of the diminished mental state at the time of the incident thus providing a purpose other than the truth of the matter asserted." Resp. at 28. This is precisely why counsel was ineffective.

Washington courts have long recognized that lay witness testimony is admissible to establish a criminal defendant's mental state as long as: (1) the witness had a sufficient acquaintance with the defendant or had sufficient time to observe the defendant; (2) the witness generally testifies as to the peculiar facts and circumstances on which his or her conclusion is based; and (3) the testimony refers to the defendant's mental condition at or close to the time the witness made the observation and at or close to the time the offense at issue occurred. State v. Stumpf, 64 Wn.App. 522, 525–26, 827 P.2d 294 (1992) (citations omitted) (holding that a period of more than three months was too long).

Here, Ms. Toste, Norm Reinhardt, and Pat Dawson all had recent information indicating that Mr. Mathes was experiencing paranoid delusions and using drugs again. The State argues that a diminished capacity defense was required to admit such evidence, but our Supreme Court recently distinguished between the expert testimony required to establish a diminished capacity defense versus relevant and admissible "observation testimony about relevant facts tending to rebut the State's mens rea evidence." State v. Clark, 187 Wn.2d 641, 651, 389 P.3d 462 (2017). The lay witness testimony was thus admissible to show that Mr. Mathes did not have the intent to perpetrate his offenses and also to support a voluntary intoxication defense. The statement to Mr. Reinhardt about wanting to commit "suicide by cop" was admissible as a statement of intent pursuant to ER 803(a)(3). See, e.g., State v. Powell, 126 Wn.2d 244, 266, 893 P.2d 615 (1995) ("the state of mind exception does allow hearsay statements to prove that the declarant acted in accordance with statements of future intent").

While the State is correct that the testimony in State v. Ramm, 198 Wn.App. 1040 (April 17, 2017) (unpublished), would have been relevant to a diminished capacity defense, such was not the case in Toth v. State, 2015 WY 86A, 38, 353 P.3d 696 (Wyo. 2015) or State v. Jensen, 251 N.W.2d 182 (N.D. 1977). In Toth, the non-hearsay statements should

have been admissible to show that the defendant "was under the influence of a controlled substance to the extent that he could not form the specific intent to deprive required for a felony conviction." Toth, 353 P.3d at 708. Jensen likewise involved an intoxication defense. 251 N.W.2d at 188-89.

The State is also incorrect in any of its contentions involving Mike Trent, who is not Ms. Toste's husband or ex-husband—such misguided belief was part of Mr. Mathes's delusional (and thus admissible) thinking.

As most, if not all, of the evidence cited in Mr. Mathes's *pro se* pleading and Supplemental Brief would have been admissible towards his intent, counsel was ineffective.

D. COUNSEL SUPPRESSED HELPFUL TESTIMONY

Counsel's exclusion of valuable evidence—which he later relied upon in closing—concerning Mr. Mathes's state of mind, intoxication, and possible lack of intent to commit certain of his offenses certainly seems to constitute ineffective assistance warranting new trial.

E. COUNSEL FAILED TO PROPERLY PREPARE DR. MUSCATEL, WHICH LED TO EXCLUSION OF HIS TESTIMONY AND THE BASIS OF THE DEFENSE THEORY OF THE CASE

Counsel's deficient preparation of Dr. Muscatel, which Dr. Muscatel even acknowledged, prevented Mr. Mathes from presenting a diminished capacity defense. This is the essence of ineffective assistance.

The State's attempt to reframe the issue by citing to inapposite cases is unavailing. See Resp. at 36-41.

First, the record is clear that counsel failed to obtain significant medical and related records detailing Mr. Mathes's longstanding struggles with mental health and substance abuse issues. Dr. Muscatel relied exclusively upon case materials and Mr. Mathes's self-reporting. See Ex. C. The State, ironically, seems to dismiss Mr. Mathes's self-reporting as to his levels of intoxication, but credit such self-reporting as to his mental health history. See Resp. at 41-42. Dr. Barnard, contrariwise, had a wealth of materials to review, and specifically provides a list in his report. See Supp. Br., Ex. K.

Dr. Muscatel expressed that he should have had all of the materials, but that he did not change his conclusions in light of the new information. Dr. Barnard, assessing Mr. Mathes afresh and armed with all of the necessary data, arrived at a different diagnosis. He was unequivocal: "Dr. Muscatel's evaluation was seriously hampered by the fact that he was not provided with the extremely important information about Mr. Mathes' extensive mental health history." See id.

The State complains that Mr. Mathes went "expert shopping," which is untrue. As explained in Mr. Suffian's Declaration, Dr. Barnard, with no disrespect meant, was literally the sole qualified practitioner that

counsel could locate who, on such short notice, was not only available to undertake the project, but also could visit the Washington State Penitentiary on one of the few days that Mr. Mathes could receive visits. He was probably the sixth or seventh person counsel tried to retain, but none of the familiar practitioners were interested. Nobody in this office or any contacts had heard of Dr. Barnard. Counsel was lucky enough to find him after an exhaustive and time-consuming internet search, and was pleased with his accessibility, intelligence, and, of course, work product.

The State also protests that Dr. Barnard's report somehow constitutes—or fails to constitute—newly discovered evidence, yet the cases it cites states otherwise. In In re Copland, the asserted ground for relief was newly discovered evidence; there was no claim of ineffective assistance. 176 Wn.App. 432, 309 P.3d 626 (2013).

While State v. Harper is closer to the mark, it is easily distinguishable: the ineffective assistance issue was whether counsel was ineffective for failing to "continue seeking out expert opinions until he found an expert who was willing to opine that Harper did meet the diminished capacity standards." 64 Wn.App. 283, 290, 823 P.2d 1137 (1992). Although the post-conviction expert conducted his own examination, he nevertheless "reviewed the same evidence from Harper's file" that the prior expert reviewed. The Court thus found that Harper

repeated a common pattern not present in this case: "the retention of new counsel, who retains a new expert, *who reviews the same evidence*, and presents a new opinion." Id. at 294 (emphasis added).

Here, Mr. Mathes presents an entirely different scenario: counsel failed to properly prepare the expert, Mr. Mathes retained a new expert, who reviewed *much more* evidence that the first expert did not have, and presented a new opinion.

It seems axiomatic that proper preparation of an expert requires all available relevant information. See, e.g., Brown v. Sternes, 304 F.3d 677, 696-97 (7th Cir. 2002) (noting it is common knowledge that an evaluating psychiatrist's expert opinion concerning a defendant's mental status will be based primarily on "past psychiatric history, family history, criminal activity, and medical records") (citations omitted). The ABA Criminal Justice Standards, which Supreme Court has long referred to "guides to determining what is reasonable," Rompilla v. Baird, 545 U.S. 374, 125 S.Ct. 2456, 2466, 162 L.Ed.2d 360 (2005), further dictate a finding of deficient performance:

> The attorney initiating an evaluation should obtain and provide … all records and other information that the attorney believes may be of assistance in facilitating a thorough evaluation … The attorney should also take appropriate measures to obtain and provide to the evaluator information that the evaluator regards as necessary for conducting a thorough evaluation on the matter(s) referred

> … Such information may include relevant medical and psychological records, social history, police and other law enforcement reports, confessions or statements made by defendant, investigative reports, autopsy reports, toxicological studies, and transcripts of pretrial hearings.

ABA Criminal Justice Standard on Mental Health 7-3.4(b).

While the State disputes Mr. Mathes's level of intoxication, the toxicology screen, Ms. Toste's testimony that he injected a controlled substance, Roy Mathes's testimony that his son was gone, and the fact that effects of methamphetamine persist for six to 24 hours—evidence which counsel could have and should have presented—there was ample evidence of serious intoxication.

There is no question that Dr. Muscatel is a well-respected and qualified practitioner. This office has actually consulted with and retained him in the past. The state, though, misconstrues his statement that Mr. Mathes was "not psychotic in his presentation" *at the time of the evaluation*. See Resp. at 42. Although Mr. Mathes's chronicled history of mental health and substance abuse issues would not establish a specific mental state on the day of the offenses, such history is certainly relevant to a mental evaluation by an expert. Lacking these materials, Dr. Muscatel found the foundations for a mental defense, but thought it was, essentially, a jury issue whether the impairment resulted in diminished capacity. This

is consistent with ERs 401, 402, and 702 and State v. Atsbeha, 142 Wn.2d 904, 16 P.3d 626 (2001) and its progeny.

Equipped with all of the materials he needed to perform a proper evaluation, Dr. Barnard arrived at a different conclusion than Dr. Muscatel. Counsel was thus ineffective in preparing Dr. Muscatel.

F. COUNSEL FAILED TO REQUEST A VOLUNTARY INTOXICATION INSTRUCTION

Counsel not only failed to request an involuntary intoxication instruction, but also failed to sufficiently develop the defense—as this Court previously acknowledged.

There was, first, sufficient evidence in the record for the instruction in the testimony of Ms. Toste and Roy Mathes.

Even assuming, *arguendo*, that there was insufficient evidence to justify the instruction, counsel was ineffective for failing to elicit additional evidence of intoxication and how that intoxication would have impacted his ability to formulate the intent to commit his offenses. In a recent case, this Court found that even where there is substantial evidence of intoxication, there must be evidence that the intoxication impacted the defendant's ability to acquire the required mental state to commit the crimes. State v. Classen, 4 Wn.App. 2d 520, 536, 422 P.3d 489 (2018). While the Court reiterated that expert testimony is not required for an

intoxication based upon alcohol because jurors are familiar with the effects of alcohol, it nevertheless concluded that "competent evidence that methamphetamine or heroin affected [a person's] ability to form the requisite mental state" was required. Id. at 537.

Here, especially once he knew that the court rejected a diminished capacity defense, counsel should have moved to admit evidence of the toxicology screen and evidence of the long-lasting duration of a methamphetamine high as well as any other relevant information about the drug and Mr. Mathes's usage and addiction. Dr. Muscatel seemed to suggest this early in the process, but counsel never followed up

G. COUNSEL FAILED TO IMPEACH MS. TOSTE AND DETECTIVE GREEN

Despite their inconsistent statements, counsel failed to properly impeach Ms. Toste and Detective Green. Ms. Toste was aware of Mr. Mathes's methamphetamine use, which the toxicology report demonstrates, and she willfully disobeyed a court order by going to his home. This failure to impeach the credibility of crucial witnesses with their inconsistent statements is ineffective assistance. See, e.g., State v. Horton, 116 Wn.App. 909, 68 P.3d 1145 (2003).

H. COUNSEL FAILED TO PROPERLY ADVISE MR. MATHES ABOUT HIS RIGHT TO TESTIFY OR NOT TESTIFY

According to his Declaration, counsel advised Mr. Mathes that all of his criminal history would be admissible if he chose to testify at trial. See Ex. A. Per his criminal history, however, only two of his convictions were within 10 years of his present offenses, one of which is a drug offense and the other was a violation of a domestic no contact order; these may or may not have been admissible. None of his other convictions seem admissible as crimes of moral turpitude. See Supp. Br. Ex.

A criminal defendant has a state and federal right against compelled self-incrimination. See, e.g., State v. Mendes, 180 Wn.2d 188, 194, 322 P.3d 791 (2014) (citing Amd. V; Const. art. I, §9). An evidentiary hearing is required when a defendant makes a sufficient showing that counsel "actually prevented" him or her testimony. State v. Robinson, 138 Wn.2d 753, 759, 982 P.2d 590 (1999). "[A]ttorneys who misinform the defendant of the consequences of taking the stand or make other misrepresentations to induce the defendant to remain silent also prevent their clients from testifying." Id. Such is the case here—in yet another example of ineffective assistance.

I. THE NUMEROUS INSTANCES OF INEFFECTIVE ASSISTANCE COLLECTIVELY MANDATE RELIEF

Given trial counsel's many deficiencies and the clear prejudice resulting therefrom, relief is mandated due to freestanding and cumulative errors. The Strickland Court, itself, seems to have made this clear: "[A] court making the prejudice inquiry must ask if the defendant has met the burden of showing that the decision reached would reasonably likely have been different absent the *errors*." 466 U.S. at 696.

III. CONCLUSION

For the foregoing reasons, Mr. Mathes respectfully requests that this Court reverse his convictions and remand for a new trial, a trial or hearing, or, at the very least—resentencing.

DATED this 26th day of November, 2018.

Respectfully submitted,

*/s/ Craig Suffian*_____
Craig Suffian, WSBA #52697
Attorney for James Mathes

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EXHIBIT A

IN THE COURT OF APPEALS FOR THE STATE OF WASHINGTON
DIVISION TWO

IN RE PERSONAL RESTRAINT PETITION OF JAMES CHARLES MATHES	DECLARATION OF JAMES MATHES IN SUPPORT OF PETITION

1. My name is James Mathes. I am the petitioner in this case. I am over the age of 18 and competent and qualified to make this declaration. I make this declaration based on my own personal knowledge and observations.

2. I was represented at trial by Ron Ness. He rarely communicated with me; did not heed my suggestions; made false promises; failed to perform a complete investigation; failed to properly advise me during plea negotiations—particularly with respect to the potential consequences of *multiple* firearm enhancements—failed to effectively represent me during trial; was ineffective through the sentencing process; and made all of his suggestions and advisements to me as based upon an incorrect offender score.

3. Although I received discovery early in the case, I was only allowed the keep the materials for 30 days. Mr. Ness never reviewed the discovery with me. He seemed more concerned about getting me to plead guilty.

4. Mr. Ness assured me that he would help address my medical issues (I was shot three times by law enforcement) while incarcerated in the Kitsap County Jail. He did not.

5. Mr. Ness assured me that he would help me gain access to the law library. He did not.

6. Throughout the entirety of the plea negotiation process, Mr. Ness never told me the statutory maximum I might face if I proceeded to trial. He also never explained that *each* firearm enhancement would necessarily run *consecutively with no good time*. My understanding was that there would be only one firearm enhancement. Rather than my understanding that I would face one 60-month firearm

enhancement, approximately 288 months of my sentence consists of firearm enhancements.

7. While I understood that I would receive 10% earned release time if convicted of assault in the first degree and that I would receive 33% earned release time if convicted of assault in the second degree, I had no idea that the firearm enhancements would be imposed consecutively and with no good time. Again, I thought that at sentencing, I would be subject to only the singular 60-month firearm enhancement on one count of assault in the first degree.

8. During plea negotiations with the State immediately prior to trial, I was advised that if I proceeded to trial, the State would add charges and that I likely would face a sentence tantamount to life. Nobody ever told me precisely how much time I might face. As I was 44 years old at the time of trial and the majority of my family members pass away before the age of 70 (usually about age 65), I viewed the sentences that would result from the plea offers as equivalent to life sentences. I never imagined—and it was inconceivable to me—that I could possibly face 720 months in prison.

9. Also during plea negotiations with the State, my understanding was that the State would add three charges if I opted for trial. The State, instead, added eight counts and many more enhancements.

10. I was prepared to plead guilty to charges that would result in a 15-20 year sentence. Had Mr. Ness properly calculated my offender score, properly negotiated, and properly advised me as to the potential ramifications of choosing trial over accepting a plea deal, the plea deal would have been closer to, if not less than, 20 years and I would have accepted the offer.

11. In between the time of arraignment and trial, Mr. Ness experienced significant medical issues and had to ask for several continuances before obtaining medical approval to participate in a trial.

12. Immediately prior to trial, Mr. Ness requested additional funds even though our retainer agreement provided that trial was included in the initial retainer.

13. During trial, Mr. Ness seemed inattentive, failed to track what was going on, and missed or erred on many key evidentiary issues. He passed away approximately 10 months after my trial.

14. Although I had been convicted of a multitude of charges with a multitude of enhancements, Mr. Ness rushed me into sentencing just days after entry of the jury verdict. We had no discussions about this. He failed to file a sentencing memorandum, [redacted] [redacted], failed to refer me for a presentence investigation, and let me be sentenced as based on an incorrect offender score which resulted in imposition of more time than legally permitted.

15. On November 22, 2018, attorney Craig Suffian visited me at the Washington State Penitentiary in Walla Walla, Washington to verify the information herein is correct and to obtain my signature.

16. Mr. Ness and I discussed whether I would testify. I wanted to testify. I chose to not testify after Mr. Ness informed me that all of my criminal history would be admissible against me. Had I known otherwise, I would have testified.

I make this declaration under the penalty of perjury and acknowledge that the statements are true and correct to the best of my knowledge and belief.

SIGNED AND DATED this 22nd day of November, 2018.

James Mathes

JAMES MATHES

17. During the one discussion we had about me possibly testifying, we never discussed the substance of my proposed testimony. Mr. Ness did not seem interested.

EXHIBIT B

IN THE COURT OF APPEALS FOR THE STATE OF WASHINGTON
DIVISION TWO

IN RE PERSONAL RESTRAINT PETITION OF JAMES CHARLES MATHES	DECLARATION OF CRAIG SUFFIAN IN SUPPORT OF PETITION

1. My name is Craig Suffian. I am over the age of 18 and competent and qualified to make this declaration. I make this declaration based on my own personal knowledge and observations.

2. I am one of Mr. Mathes's attorneys. I initially met with him at the Washington State Penitentiary on April 21, 2018. We discussed his case, the issues he had already diagnosed and presented, and his thoughts about his case and how to proceed. He specifically mentioned the plea advisements and his lack of understanding as to the mandatory, consecutive nature of the firearm enhancements.

3. After our meeting, my first priority was to ask this Court for leave to supplemental him *pro se* filing and then find a mental health professional who had the time to review the case materials and other records as well as evaluate him at the facility. I contacted numerous practitioners with whom our office works, but none were available. This was not the quickest process. I actually had one expert accept the undertaking only to decline when he discovered the limited days he could visit the prison. I then began contacting referrals, but to no avail. I then conducted basic internet research in hopes of finding a practitioner on the East side of the state and after a few unsuccessful attempts with others, I connected with Dr. Barnard. As neither I nor anybody else in our office (or any of our contacts) was familiar with Dr. Barnard, we were leery to retain him. Time, though, was of the essence, and he was available so we agreed to retain him. Far from expert shopping, then, the choice of Dr. Barnard was pure exigency.

4. I have maintained regular contact with Mr. Mathes. Throughout the duration of this representation, he has always been consistent in what he expresses—especially as to his lack of understanding of his maximum standard range sentence and the firearm enhancements. He has stated that had he known that he might face 720 months of

incarceration, he likely would have accepted a plea offer to approximately 25 or less years.

5. I intended to visit Mr. Mathes again before filing the Supplemental Brief. Due to my schedule, the fact that I am based in Seattle while Mr. Mathes is housed on the other side of the state, and the few days available for visitation, I was unable to do so. I determined that I would visit him before we filed the Reply in order to get a signed Declaration from him. I was hoping that his *pro se* pleading, the representations in the Supplemental Brief, and Petitioner's Verification would suffice, but the State's Response makes clear the State's position that evidence of counsel's deficient advisements is lacking.

6. During my visit with Mr. Mathes on November 22, 2018, I obtained a Declaration from him that was consistent with everything he had previously relayed to me. I, however, had not asked him about his decision to not testify and the nature of his discussions with counsel. I was dismayed that counsel seems to have effectively and actually prevented him from testifying.

I make this declaration under the penalty of perjury and acknowledge that the statements are true and correct to the best of my knowledge and belief.

SIGNED AND DATED this 26th day of November, 2018.

*/s/ Craig Suffian*__
CRAIG SUFFIAN

EXHIBIT C

Kenneth Muscatel, Ph.D. tel/fax: (206) 324-4443/e-mail: kmuscatel@msn.com
Clinical, Forensic and Neuropsychology
1001 Broadway, Suite 318
Seattle, Washington 98122-4304

Forensic Psychological Evaluation

NAME: James Mathes
DATE OF BIRTH: 4-21-1969
PSYCHOLOGICAL TESTS: Personality Assessment Inventory (PAI); Beck Depression Inventory-II (BDI-II); Beck Anxiety Inventory (BAI)
MARITAL STATUS: Divorced
AGE: 45
EDUCATION: 11+ years, no special education, GED
REFERRED BY: Ron Ness, attorney for Mr. Mathes
DATE OF EXAMINATION: 11-17-2014
DATE OF REPORT: 12-16-2014
CAUSE NUMBER: 14-1-0030101

REASON FOR REFERRAL

The purpose for the examination is to evaluate Mr. Mathes' mental state at the time of the alleged offense. I interviewed him at the Kitsap County Jail

PSYCHOLOGICAL TEST RESULTS

The Beck Depression Inventory-II (BDI-II) examines symptoms and complaints associated with clinical depression. The subject obtained a score of 23 out of 63 possible units, a result that suggests endorsement of moderate and significant complaints of clinical depression. This included feeling as if he is being punished, feeling disappointed in himself, having a loss of interest in sex, having difficulty concentrating and having a loss of appetite. He reports some sleep disturbance and is very self-critical, with perception of his past failures and pessimism about the future.

The Beck Anxiety Inventory (BAI) examines symptoms and complaints associated with clinical anxiety disorder. The subject obtained a score of 7 out of 63 possible units, a result that suggests endorsement of minimal and probably no significant complaints of clinical anxiety. He only endorsed feeling nervous and unable to relax to any significant degree.

The Personality Assessment Inventory (PAI) was administered. The formal diagnostic assessment based the PAI results is not available because too many item responses were omitted (>5%). This was because he tended to answer some

items with endorsement of more than one response, making that item not scoreable. Thus, the interpretation of these results is offered with some caution.

The available results of the PAI did indicate no elevation in Negative Impression Management and very low Positive Impression Management. This means he doesn't tend to present himself in a negative manner, but did not endorse positive behavioral and mental health features he might possess He endorsed a substantial amount of traumatic stress in his life, elevated health concerns, not a great deal of anxiety aside from the traumatic stress already noted, marginal cognitive features of depression, with some marginal physiological features of depression, but marked hypervigilance (but without feelings of persecution or resentment) that suggest significant paranoia and possible delusional thoughts and feelings. He endorsed borderline personality features, with affective instability, negative relationships, and self-harm elements noted. He has identity problems noted as well. There is evidence of disordered thinking. He endorsed responses consistent with anti-social behavior. He endorsed responses indicated an aggressive attitude and physical aggression, and a great deal of stress in his life. Most prominent by far in this set of results was the presence of alcohol and drug problems (t-score 102 and 108 respectively).

He appears to have elements of paranoid thoughts and feelings, stress and trauma in his recent life, and a history of unstable relationships and affective instability. His history of drug and alcohol abuse are likely extremely significant and notable.

BEHAVIORAL OBSERVATIONS AND INTERVIEW

The subject was informed about the non-confidential nature of the examination. He understood the informed consent and agreed to proceed with the examination. The subject understood he was not my patient and I was not providing treatment. He understood anything discussed or disclosed in our examination could be part of this report, understood he was free to decline to answer any question and could takes breaks as needed (although given the setting the opportunity to take a break was limited).

Mr. Mathes dropped out of high school his senior year but completed a GED at McNeil Island. He has been in prison four times, most recently in 2005-06, when he served eighteen months at Stafford Creek for possession of heroin and methamphetamine. Prior to that, from 1997 to 2001 he served fifty four months at Walla Walla and McNeil Island for third degree assault, including an assault on the Washington State Patrol officer, violation of a no contract order, an ignition interlock violation, and other infractions. Prior to that he served a year at McNeil Island, on third degree assault and felony possession of marijuana charges. His

first criminal violated resulted in a sentence of a year and a day and he served at Progress House and work release, in 1994.

He has no history of special education and indicated he reads adequately. He has never served in the military. His traditional work was varied, including harvesting forestry goods and working as a mechanic. He last worked was as a mechanic's helper for Rick's Roadside. He said he worked for himself as a roadside mechanic during that period as well.

He has received disability from Social Security (SSI and SSA) since 1996 for mental health difficulties. This included Bipolar Disorder with explosive personality features, and was more recently re-diagnosed as being schizophrenic in 2000 at Kitsap Mental Health. He was assessed with having Attention Deficit and Hyperactivity Disorder (ADHD) and Post-Traumatic Stress Disorder (PTSD), particularly after this most recent incident. He noted that he still finds it distressing if he sees someone shot on TV, but his PTSD symptoms have greatly improved with the combination of medications he currently takes, including the hydrozycine, which helps him go right back to sleep if he wakes up in the night.

He was in the hospital in 1990 for two or three weeks in Tacoma. He said he had been on high on crank for a year, and became crazy and paranoid, and committed him to the hospital. He started at Kitsap Mental Health in 1996. He got out of prison in 2000 and obtained sobriety in 2005. He said he had a few suicide attempts, including a couple overdoses. He said he tried to hang himself once when he was eighteen. When he was twenty two or twenty three he overdosed on a full bottle of nortriptyline.

His current medications include Seroquel, trazodone, clonidine, Prazosin and hydroxyzine (Vistaril). He noted the Prazosin was very helpful for the "horrible dreams" he had after the incident, including his being shot.

Mr. Mathes said he had his first drink at age ten or eleven, and started drinking regularly at age sixteen. Daily use of marijuana stated at age thirteen. He used meth on a daily basis at sixteen, at that time snorting or eating the drug. He used hallucinogenic, including mescaline, LSD and mushrooms. He has never used Sherm. His first IV use was slamming meth and heroin at twenty six or twenty seven. He was smoking heroin as well. He used the drugs together, and also was using "massive marijuana and massive alcohol" at that time. He said he likes opiates and took pills, including Demerol, OxyContin (and probably Oxycodone) and other pills of a similar nature between ages twenty five and thirty years of age. He also used benzodiazepine (anti-anxiety) medications.

He has participated in six to eight inpatient drug treatment programs, but only finished one, in 2005. However, this led to eight and a half years of sobriety, ending on 9-10-13. He had previous periods of sobriety for extended periods, including a couple each of around two years, and three periods of sobriety for about a year each time.

The most recent relapse was on 9-10-13. He and his girlfriend had been together for seven years, but he was accused of assaulting her. He said for the first three or four years she was "insanely jealous" that he was interested in other women, but after that he became the one who was insanely jealous. He declined to discuss the allegation that he hit her, but said his daughter and step-daughter were the ones who called the police. Afterwards he went to the Clearwater Casino, was drinking (double Black Velvet on ice), and feeling remorseful and guilty. He left the casino and went to his cousin's house around 4:30 AM.

He said he passed out and woke up five hours later with a terrible headache and hangover. He said his cousin offered him a fifth of vodka he had in his car and they drank nearly all of it. He said he asked his cousin to take him to a friend's house and he did drugs there, probably meth. He said his friend wasn't a "needle guy", so they just smoked. He said he stayed high for five or six days, including on heroin and meth, and a half-gallon of hard liquor a day, and didn't go to work during that period. He said he just spent the days getting loaded.

He indicated he was depressed and noted the cops were still looking for him, and decided he had had enough, so make a suicide attempt, taking pills of Seroquel, chased by Black Velvet. He did this in the parking lot of a Wal-Mart, then drove to his mother's house, passing out in her driveway. He said he was taken to St. Anthony's Hospital and was in a coma for three days, after which he was taken to jail for four or five days until he bailed out. This was in late September by his best recollection.

He said he didn't drink for a couple days, but went back to drinking a half gallon of Black Velvet whiskey, crawling into bed and getting hammered. He noted there was a no-contact order with his girlfriend at the time, but she continued to come to his house and said she told him she wanted to marry him, that he was the only man for her. He said she would come by his place four or five nights a week, stating for weeks her (or his – it wasn't clear to me) would pick her up and take her bake.

He said he rallied somewhat, stopped drinking and continued shooting meth and heroin on a daily basis. This was in early October, by his best (rather unclear) recollection. He did return to work in forestry good and some

mechanic's work. He said people were telling him he had to sober up, and he would stop using for four or five days at a time, but always relapsed.

He said in mid-October he started hearing people talking outside his trailer. He thought these were people connected to his girlfriend and thought maybe she was angry with him. He said he believed these were "dope people" who were outside his house (trailer), who he could hear talking. He said his aunt came by and confirmed there were "a bunch of weirdoes" in his yard in the middle of the night.

He said he started to think and to hear people crawling under his trailer, and he even crawled under his trailer to see if he could find them. He said he found "clean spots" on the plastic sheeting under the trailer which told him people had been there, spying on him. He said he could hear them through a hole in the floor by the shower, and he would the walls moving/vibrating as they were "screaming and humping". He said he has a pit bull but the dog spent much of time sleep, and he thought the dog was given Benadryl tablets, stating, "They've been dose-ing my dog with Benadryl". When I asked who was doing this he said it was his girlfriend and "the people she been fucking" and who were messing with him. He said one time he woke up and found his girlfriend had fallen off his couch, onto her back. He said he didn't let her out of his sight, and this time the dog was not drugged with Benadryl and was "freaking out", so who knew people were "fucking with (him) and his house".

He said one time he went to the store with his dog, and when they returned he dog started growling and barking at the floor and "freaking out". He said there was someone under the floor, and he could hear them talking and laughing. He said there were two to four different voices. This was around the end of October.

He said to me, "I know they're there" and stated his girl was coming to see him every other day and "she's part of it". He added he got into some "bad dope" around that time, once on crank and once on heroin. He subsequently suffered a bout of pancreatitis and was in the Harrison Hospital for five days, but was given pain medication and improved. He said he called his father to check out his house and said as soon as he pulled up to his place the noise stopped, but as soon as he left it started up again. He said it continued every night but if it rained hard on a night they would "take a night off". He said he could hear calls pulling up in front of his house/trailer and see the headlights at the end of his driveway. He said in the morning he would hear them leave, taking off through the brush.

He said he told his mother this was really happening and he wasn't crazy. He moved to his mom's place in mid-November and stayed there for five or six days, and during that time heard "no noise, no voices, not (even any) barking".

He said he returned to his place, and he had been sober during this period, and when he goes home he hears cars pulling up again. He said it was his girl and a couple of dope dealers, and a couple of other girls, and he said he thought he could her his girlfriend telling the others, "I want to get naked and get freaky and rub it in his face as much as I can." He said his would was bugged by his girlfriend, my mom and his dad. He said he was in his bedroom and he heard noise at the front of the house and ran over. It was the middle of the night. He said they were monitoring him. He said he looked out and could see people running into the brush.

He said his girl was always well groomed but when she came over the next time (soon afterwards) "half her nails are busted off" and "she looks like shit", which to him confirmed she was one of the people running through the woods. He said she denied it, but said she was Bipolar I and had multiple sexual partners, and he noted her pupils were "huge" and she was obviously high on something. He said he was high too, on speed, and opined his mother was high too.

He said he was convinced that people were messing with him, and opined his girlfriend was having "wild, circus sex" all the time in November and early December. He said he spent Thanksgiving with his ex-wife and five year old son. He said later his girl told him she needed money for sex. He said Christmas cam and she didn't want him to come over to her place. He got drugs and spent Christmas alone. He said at this point she told him she couldn't be with him anymore because he had to sober up.

On December 30th (although he first said on the 31st he said she was dropped by her daughter at around 5 or 6 PM, and they got "naked and freaky" for a saw hours. He said around 10 or 11 PM her daughter (Stephanie) was supposed to come get her. He said "one thing led to another and we got into a situation (and) I want to know the truth". He said she told him, "Everything you've been imagining is true". He said he "completely freaked out". He said she told him she was four months pregnant with someone else's baby and she had gone to Las Vegas and got married to some guy she worked with, who didn't know she was at his (Mathes') house. Mathes said he saw headlights in the driveway and she his girlfriend told him this man bought a 9 mm gun and was planning on killing Mathes "at his first opportunity". He said she also told him the dope dealer had a 32 caliber handgun that he was going to kill Mathes with. He said they were videoing the "weird sex shit" she was doing with these individuals and selling it over the internet.

He said that night he had taken a gram of heroin and had been awake for four or five days on heroin and meth. He said her daughter called over and "freaks out", saying she had to go home. He said this was at about 4 AM on the 31st. He said

went out to his car (it was dark out) to get his dope out of his car, but can't find it, and said he thought there were people outside waiting to get a shot at him. He said his girlfriend told him they were most likely going to try to shoot him when they were "humping". He said at that time he took a quarter gram of meth at one time IV, which he described as a "massive shot". He said they had sex for another couple hours and then her daughter showed up and said his girlfriend told her daughter to come back in another two hours.

At that point it is starting to get light out (he guessed it was around 7 AM). He said he was getting very paranoid about people shooting him, due to what he said his girlfriend told him earlier. He said she said she had a mention of a gun he (Mathes) had for self-defense. He said he finally became so paranoid and fearful he told his girlfriend they had to leave in his car, telling her "We got to take off."

He said there was a drone in the air following them and a helicopter too. He said she was looking up into the sky. He said her daughter was calling her and she was high on crank. He said he pulled the battery out of his phone because that was how he was being followed. He said he didn't really they were being followed by the drone at first because it was in "silent mode" and he couldn't hear it. He said he was driving about 100 MPH trying to avoid the drone, at one point stopping and jumping out of the car. He still can't see it but says he can now hear it on the other side of the tree line.

He said he was convinced at the point the police were trying to kill him. He said he had several assault charges in the past, including against police. He said he felt panicked and called his dad, but couldn't reach him. He said he called a friend and asked the friend to have his dad call him (Mr. Mathes).

He estimated they reached his mother's house at around 12:30 in the noon hour. He said his dad showed up as well, and is talking to his Michelle (aka Shelly), "high as hell". He said he kept peeking out the windows, convinced they were going to try and kill him at any time. He said his father came back into the house and told him "there is a better way" and said his father admitted "his part in the gang of people who's fucking with me." He said his mother and girlfriend were in with this group and he told his dad that his girlfriend was pregnant with "some dude's kid".

He said at that point the phone rang and it was the police, which he could tell by the caller ID. He said the voice on the phone asked if there was a man with a gun holding a woman hostage, and that his mother (or Michelle) said, "No." He said the officer said they were going to send someone over to check things out.

He said at that point he felt his life was over. His relationship was over, he had sold everything he had and his life was "completely destroy". I noted at this point in the interview his speech, while always pressure and rambling, became even more pressured and disjointed. He said he still thought there were dope dealers outside and hiding under the house, waiting to shoot him.

He said he told his dad, Michelle and Stephanie, "Let's get out of here". He said they exited the house and he saw the police outside, with "rifles and pistols". He said the put the gun down (lowered the gun in his hand) so it was not visible. He said he jumped into his car "to get the fuck out of here". He said he felt like everything had gone wrong, with his nine years of sobriety in ruins after his relapse, and said, "I've had enough". He said he didn't want to die but "I'm doing what I'm doing. I don't care." He said he jumped out of the car, the pistol still in his hand.

He said he heard the gun go off. He recalled glass blowing out of his car and he was "spinning in circles". He said he didn't feel himself being hit by bullets. He said he passed out for a couple minutes after coming to he realized "I'm shot full of holes". I asked if he remembered firing his gun and he replied that he thinks he was shot in the arm and the gun went off. He recalled lying on the ground, "coughing out my lungs. I'm dead."

He said he had been started on a new medication regimen in June or July, what he said was an ADHD medication. He said he told his doctor it wasn't working, that it was making him more paranoid and restless, and he said he was sleeping only a couple hours a night and was working fourteen to sixteen hours a day. He said because of these complaints that actually doubled his dose of the medication, and he became even more paranoid. He said he was no longer given more than a couple weeks worth of Seroquel, as the ADHD medication caused him to become more paranoid.

He said a couple weeks before the incident he went off all his medications and everything went "fucking haywire". He said his concentration worsened, he became "paranoid as hell", and was hearing and seeing things.

REVIEW RECORDS

I reviewed the discovery in this case provided by Mr. Ness. Besides the many investigative reports, I review the transcripts of statements provided by Ms. Toste (12-18-13 and 1-9-14); the statement by Ms. Hanna Caulder dated 12-31-13 and the statement by Roy Mathes (father of the defendant) dated 12-31-13. I reviewed the DV - No Contact Order dated 9-17-13 which directed and restricted Mr. Mathes from having any contact with Ms. Toste. I reviewed a medical

records concerning James Mathes (spelled Mathis in these records) following the gunshot injuries he suffered during the incident/his arrest.

The witnesses indicate Mr. Mathes had a handgun in his possession and fired first. Michelle Toste indicated in her handwritten statement dated 1-15-14 that she was held hostage at gunpoint all night until the following afternoon. She said Mr. Mathes pointed the gun at her head most of the time, and wouldn't let her call anyone except his mother. She said he "physically, emotionally and mentally destroyed (her)". She alleged he told her if anyone called the cops he would shoot her, and if she was lucky she might see her kids again (including a child they had together). She indicated she was scared for her life because of what he did, and opined he should be put in jail for a very long time.

FINDINGS AND OPINION

Mr. Mathes appears to have chronic mental health problems of a very serious nature, with causes likely due to constitutional factors but also exacerbated by and exacerbating severe substance abuse problems. He reported being sober for several years from the mid-2000's until only a couple years ago, but relapsed severely, using alcohol, methamphetamine and heroin, including intravenously. From that point on his mental health, work and interpersonal behavior dramatically deteriorated.

In the incident Mr. Mathes reported paranoid symptoms and delusional thoughts and feelings of a highly acute nature. It appears his paranoia, and the secondary confusion and disorganization caused by drug abuse, is responsible for his aggressive, confused and disorganized behavior in the incident that resulted in his being shot by the police. It was evident in our interview and in the reports and other documents I reviewed in this case that his thinking was disturbed, impaired and delusional, and those impairments likely were the cause of his actions that day. The day of the incident he believed he was being threatened by people who wanted to kill him, was being tracked and monitored by drones, and thought his girlfriend was associated, sexually and otherwise, by those people who wanted to harm him. This disturbed, confused and psychotic mental state reflected both chronic mental health impairments and the obvious effects of chronic abuse of meth, heroin and alcohol.

The evidence of this case indicates that he was highly intoxicated in and around the time of the incident. Although his chronic, un-intoxicated mental state was likely impaired to a significant degree at the time of the incident, his level of drug abuse toxicity was the larger source of his acute paranoia, and delusional thoughts, feelings and auditory hallucinations. Because of this, a potential defense of legal insanity is probably not available.

Rather, impairment of mental functions secondary to the direct effects of drugs and alcohol indicate the only available mental defense to be Diminished Capacity. In Diminished Capacity an individual would be found innocent if unable to form the specific and requisite intent in the charged offense.

In terms of forming general intent, there appears to be insufficient impairment to prevent him from engaging in the intentional behavior of threatening the family members and his ex-girlfriend with the gun or trying to leave the scene after the police arrived. He asserted that the gun discharge accidentally or unintentionally, and therefore he did not intend to shoot it.

The material I reviewed suggests Mr. Mathes was acutely psychotic and delusional at the time of the incident, and had beliefs about his girlfriend and family that were grossly distorted – that they intended to kill him. It appears he also believed he was being stalked and monitored by drones and drug dealers associated with his ex-girlfriend were trying to kill him. Thus, while his behavior was clearly intentional in the general sense, this scenario raises the question of whether his mental disturbance prevented him for forming the requisite intent to commit the charged offenses, if he erroneously believed due to his mental disease and defect (chronic mental illness and the acute effects of drug-induced psychosis) that he was acting in some form of self-defense when he threatened Ms. Toste and others with the gun, and attempted to leave the scene that was surrounded by the police. If he believed he was going to be killed unless he left the scene, his actions could be construed as attempting to defend himself, as bizarre and disturbed as that may sound to the outside observer.

The evidence in this case is less than clear, particularly about how his gun discharged and whether he was shooting at the officers. If it was concluded by the trier of fact he was shooting at the officers, he clearly would have been able to form the intent to commit that specific act. His ability to understand he was committing a crime in the house if he believed he was defending him is much less clear.

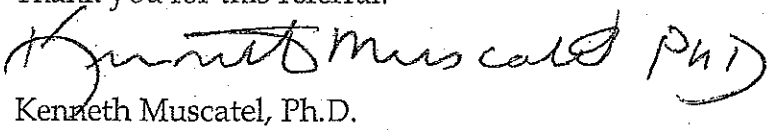
Thus, overall it remains unclear whether he lacked the capacity to commit the requisite intentional acts. However, there is abundant evident of foundation to raise the defense of Diminished Capacity and argue this defense at trial. Whether it is found viable will depend on assessment of the facts – the why, how and what happened – and whether those facts suggest he could form the specific, requisite intents of the various charges.

Diagnosis (DSM-V)

- Amphetamine Abuse/Addiction
- Heroin Abuse/Addiction

- Alcohol Use Disorder - severe
- Unspecified Psychotic Disorder – but paranoid and delusional features noted – both associated with chronic mental health impairment and exacerbated by his sustained and severe substance abuse
- Unspecified Depressive Disorder
- Unspecified Personality Disorder – with paranoid and anti-social features noted

Thank you for this referral.



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Clinical, Forensic and
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EXHIBIT D

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Facts about Methamphetamine

Methamphetamine is commonly known as "speed," "meth," and "chalk." In its smoked form it is often referred to as "ice," "crystal," "crank," and "glass." Methamphetamine is a Schedule II stimulant, which means it has a high potential for abuse and is available only through a prescription that cannot be refilled. There are a few accepted medical reasons for its use, such as the treatment of narcolepsy, attention deficit disorder, and for short-term use-obesity; but these medical uses are limited.

It is a man-made stimulant and the bulk of methamphetamine currently on the streets has been illegally manufactured. The chemicals used in the manufacturing process can be corrosive, explosive, flammable, toxic, and, possibly, radioactive. For every pound of finished product, 5 or 6 pounds of chemical waste is left at the illicit lab site.

There are currently three types of methamphetamine:

1. L-methamphetamine (*Levo-methamphetamine*) raises the blood pressure and causes the heart to beat rapidly, but does not increase alertness very much. Shakes/tremors and stomach cramps are common physical side-effects.

2. D/L-methamphetamine (*Dextro-levo methamphetamine*) is made with the amalgam (P2P) method. It was popular during the 1960s, but it is still made and distributed. It has to be injected to get the desired rush and produces side effects such as shakes, tremors, and stomach cramps.

3. D-methamphetamine (*Dextro-methamphetamine*) is currently the most common. It is made by the ephedrine reduction process. It is 2 to 10 times as physiologically active as L-methamphetamine. It increases the heart rate, blood pressure, body temperature, and rate of breathing and dilates the pupils, and has fewer adverse side effects than the other two types of methamphetamine.

The term "ice" most often refers to a pure form of d-methamphetamine HCl. "Ice," also known as crystal meth, is a smokeable form of methamphetamine. It is a large, usually clear crystal of high purity that is smoked in a glass pipe. The smoke is odorless, leaves a residue that can be resmoked, and produces effects that may continue for 12 hours or more.

Methamphetamine comes in pill, powder, clear liquid, and rock form (that resembles a block of paraffin). The coloration of methamphetamine may vary significantly due to the manufacturing process and as a result, it may have a foul rancid odor. Possible colors include: colorless/white, red, orange, purple, green, and brown.

Methamphetamine is most often used in a "binge and crash" pattern. Tolerance for methamphetamine occurs within minutes. The pleasurable effects begin to disappear even before the drug concentration in the blood falls significantly. Users try to maintain the high by binging on the drug.

Identifying Abuse

- Users are referred to as a Meth head (regular user), Meth monster (one who has a violent reaction to methamphetamine), or Speed freak (habitual user of methamphetamine).
- The person may exhibit anxiousness; nervousness; incessant talking; extreme moodiness and irritability; purposelessness; repetitious behavior such as picking at skin or pulling out hair; sleep disturbances; false sense of confidence and power; aggressive or violent behavior; disinterest in previously enjoyed activities; and severe depression.
- A person using alcohol while on methamphetamine, during the "tweaking" stage, can be identified by looking at their eyes. Their eyes will jerk back and forth when they look out of the corner of their eyes (a horizontal-gaze nystagmus).
- The chronic user of powdered methamphetamine is often undernourished with a gaunt appearance, poor hygiene, and bad teeth. Chronic abusers are violent and suffer rapid mood swings, with behavior going from friendly to hostile in seconds.
- If an abuser has taken a lethal dose of d-methamphetamine, the heart rate will rapidly increase and the abuser will collapse and suffer a heart attack or a stroke. The only overt signs of overdose are an abnormally high temperature or the symptoms of a heart attack or stroke.

Methamphetamine's high lasts anywhere from 8 to 24 hours, and 50 percent of the drug is removed from the body in 12 hours; Methamphetamine will stay in the plasma between 4 to 6 hours; it can be detected in the urine one hour after use and up to 72 hours after use; Methamphetamine metabolites can be detected in the body for 2 to 4 days.

Methamphetamine is typically used on a regular daily basis and users tend to integrate their drug use into many of their daily activities. Withdrawal frequently doesn't occur for 90 days from the time of the last use, making treatment a long-time process. The most effective treatments for methamphetamine addiction are cognitive behavioral interventions. These approaches are designed to help modify the patient's thinking, expectancies, and behaviors and to increase skills in coping with various life stressors. The 12 step program has been shown to have the greatest success rate among methamphetamine users.

If you or a family member is experiencing a mental health or an alcohol or other drug-related emergency, seek immediate assistance by calling the24-hour Suicide Prevention, Mental Health Crisis, Information and Referral Hotline: (216) 623-6888 or the United Way's First Call for Help, 211 or (216) 436-2000.

How Long Does Meth Last?

Meth is a highly addictive stimulant with effects that last six to 12 hours or longer. People who use the drug go through several distinct stages of intoxication. Those who smoke or inject the drug feel the fastest and most intense high.

TOPICS ON THIS PAGE

- Stages of the High
- Effects by Method of Use
- Meth Metabolism

Author: Amy Keller, RN, BSN | **Last Updated: 5/18/18**

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Methamphetamine, or crystal meth, produces an energetic feeling of euphoria that is similar to a cocaine high, but the effects of meth last longer.

Meth Treatment

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The rush from snorting cocaine usually lasts 15 minutes to a half hour, and a crack high lasts no more than five to 10 minutes. The intoxicating effects of meth, however, typically persist for eight to 24 hours.

Estimates of the precise length of a crystal meth high vary widely. Some researchers have found that the stimulant effects of the drug last approximately six to eight hours. A National Institute of Justice report states that they can last 12 to 14 hours or longer. Other sources report that the high can last up to 24 hours.

Stages of Meth Intoxication

A person goes through several distinct stages of intoxication after consuming meth. The stages may vary depending upon the method of use, the dose taken and whether or not the individual has a meth addiction.

Break the chains of addiction

LET US SHOW YOU HOW

The Rush

The rush, or “flash” as it’s sometimes called, is the intense euphoria a person feels within seconds of injecting or smoking meth. The rush comes from a sudden flood of the pleasure chemical dopamine in the brain.

During a meth rush, the heart rate quickens, pupils dilate, blood pressure soars and metabolism kicks up several notches. The feeling of a meth rush has been compared to having multiple

orgasms.

This intense phase usually ends in five minutes, but it can last up to half an hour. A person won't feel a flash when snorting meth or swallowing it.

The High

After the rush passes, a person will shift into a less intense state of euphoria that could last from four to 14 hours. This stage, sometimes called "the shoulder," is characterized by hyperactivity and rapid thinking.

Some people may exhibit argumentative, aggressive or obsessive-compulsive behavior while high. They may seem confused, and their speech might not make sense.

The Binge

Bingeing describes repeatedly using a drug for days at a time to stay high. Engaging in a meth binge can cause severe insomnia for days on end. Some people also forgo eating. It is common for meth users to consume the drug in a pattern called binge and crash.

The Crash

Bingeing eventually culminates in a dramatic crash, or comedown, when the person stops feeling a rush from the drug or runs out of meth. The crash is associated with extreme exhaustion and long periods of sleep.

Tweaking

Tweaking is considered the most dangerous stage of meth abuse. According to the University of Maryland's Center for Substance Abuse Research, tweaking occurs when a meth user goes several days without sleep and starts to grow increasingly frustrated, paranoid and unstable.

People are unpredictable during a tweaking episode. Their eyes may dart around, and they may become violent. During this stage, they may lose touch with reality and develop meth psychosis.

Strong cravings for more meth are common in the tweaking phase, but the high from taking the drug starts to become less powerful. People who are tweaking have been known to go about 15 to 40 days without any sleep.

Effects by Method of Use

Some methods of use cause a quicker high. Smoking or shooting meth causes a nearly immediate high. That's because the drug enters the brain more rapidly when it's inhaled or injected directly into the bloodstream.

When meth is snorted up the nose or swallowed, however, it can take several minutes to feel the effects. Swallowing meth is the least efficient method of getting high because it must first pass through the digestive tract.

Onset of Crystal Meth Intoxication:

- Smoking or Injecting Meth
- Effects felt within five to 10 seconds
- Snorting Meth
- Effects felt within three to five minutes
- Swallowing Meth
- Effects felt within 15 to 20 minutes

Source: National Institute on Drug Abuse

No matter how it's used, methamphetamine is profoundly addictive. When people use crystal meth repeatedly, it changes their brain chemistry.

The drug activates the reward centers of the brain, causing strong cravings for meth. Over time, the brain becomes desensitized to the flood of dopamine triggered by meth use.

As a result, people require larger amounts of the drug to feel the same high they originally experienced. This is known as developing a tolerance.

Meth tolerance can occur within minutes, and the euphoria can vanish before levels of the drug in the blood have dropped.

Meth Metabolism

While the stimulant can be only be detected in a person's blood for approximately four to six hours, meth stays in a person's body considerably longer.

The half-life of the drug is approximately 12 hours, meaning that about half of the dose is eliminated after 12 hours. About a quarter of the dose remains one day after last use.

Crystal meth can be detected in a person's urine for up to three days, or even longer with heavy use of the drug. Traces of meth can be found in person's hair for up to 90 days.

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Methamphetamine-Associated Psychosis

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Abstract

Methamphetamine (METH) is a frequent drug of abuse in U.S. populations and commonly associated with psychosis. This may be a factor in frequent criminal justice referrals and lengthy treatment required by METH users. Persecutory delusions and auditory hallucinations are the most consistent symptoms of METH-associated psychosis (MAP). MAP has largely been studied in Asian populations and risk factors have varied across studies. Duration, frequency and amount of use as well as sexual abuse, family history, other substance use, and co-occurring personality and mood disorders are risk factors for MAP. MAP may be unique with its long duration of psychosis and recurrence without relapse to METH. Seven candidate genes have been identified that may be associated with MAP. Six of these genes are also associated with susceptibility, symptoms, or treatment of schizophrenia and most are linked to glutamatergic neurotransmission. Animal studies of pre-pulse inhibition, attenuation of social interaction, and stereotypy and alterations in locomotion are used to study MAP in rodents. Employing various models, rodent studies have identified neuroanatomical and neurochemical changes associated with METH use. Throughout this review, we identify key gaps in our understanding of MAP and suggest potential directions for future research.

Keywords: Candidate genes, Drug addiction, Methamphetamine, Psychotic symptoms, Schizophrenia, Substance use disorder

Introduction

Methamphetamine (METH), a member of the amphetamine family of drugs of abuse, is easily manufactured and readily available in the USA. In 2008, approximately 13,000,000 or 5% of persons age 12 and older in the USA reported having used METH in their lifetime. While this decrease from 6.5% in 2002 (NSDUH 2009) is significant, subgroups remain particularly vulnerable to METH use disorders (MUD). For example, rural persons are more likely to use the drug than persons in either small or large metropolitan areas; and a recent analysis of the National Survey on Drug Use and Health noted that METH use increased as the setting became more rural (Lambert et al. 2008). Of concern, young adults in rural areas were nearly twice as likely as their urban counterparts (2.9 versus 1.5%, $p < 0.001$) to have used METH. Additionally, non-Hispanic whites entering Substance Use Disorders (SUD) treatment are most likely to identify opiates and marijuana as their illicit drugs of choice; whereas, Hispanic and Asian Americans are more likely to identify METH/amphetamine as their primary drug of choice (SAMHSA 2009). Lastly, gay and bisexual men use METH at much higher rates than other populations (Shoptaw et al. 2003). Significantly, U.S. youth had the second highest rate of amphetamine use worldwide in 2007 (UNODC 2009). Additionally, persons with METH use disorders entering SUD treatment are more likely to be referred by the criminal justice system than all other SUD admissions combined (59 versus 38%) and over twice as likely to receive long-term residential treatment than all other admissions (17 versus 8%) (SAMHSA 2009). It is unknown why METH use results in greater criminal justice-related admissions or longer treatment stays, but drug-associated psychotic symptoms may have a role in the drug's unique behavioral effects. While amphetamines such as METH can precipitate and exacerbate psychotic symptoms in persons with schizophrenia (Batki and Harris 2004), it has long been recognized that such drug use can produce psychotic symptoms even in persons with no history of a primary psychotic disorder (Chen et al. 2003; McKetin et al. 2006). With these issues in mind, the goals of this review are to describe the risk factors, frequency, symptoms, and clinical implications of METH-associated psychosis (MAP), discuss candidate genes with significant associations, and review preclinical animal research that aims to simulate an understanding of MAP. Within each of these areas, we will discuss gaps in our current knowledge and potential directions for future research.

Clinical features

Natural history and epidemiology of MAP

METH, cocaine, cannabis, alcohol, hallucinogens, sedatives, and heroin have all been implicated in substance-induced psychosis (Caton et al. 2005; van Os et al. 2002; Fergusson et al. 2003; Arseneault et al. 2004; Manschreck et al. 1988). Historical features such as psychotic symptoms presenting before onset of substantial substance use or psychotic symptoms only occurring in the context of substance use are useful in establishing a diagnosis. However, in many clinical settings the history is less clear and discriminating between psychoses that are secondary to substance use such as METH and those that are primary psychotic illnesses in a substance-using individual can be diagnostically challenging. In a study of 400 subjects recruited from five psychiatric emergency departments with at least one psychotic symptom and some substance use in the previous 30 days, 44% of subjects were diagnosed with a substance-induced psychosis while 56% were diagnosed with primary psychosis. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM), which employs the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for psychotic disorders, was utilized to discriminate between substance-induced and primary psychosis. Of note, a diagnosis of primary psychosis was made if there was "no evidence of heavy substance use or withdrawal, when psychotic symptoms persisted for at least 4 weeks in the absence of heavy substance use, or when psychotic symptoms preceded onset of heavy use." Parental substance abuse, drug dependence (rather than abuse or use), and visual hallucinations were predictive of a substance-induced psychosis. Additionally, persons with substance-induced psychosis had lower Positive and Negative Syndrome Scale (PANSS) scores, greater awareness of psychotic symptoms and were more likely to have suicidal

ideation (Caton et al. 2005). Similarly, in a small study ($N = 19$) of stimulant (cocaine or amphetamine) abusers seen in an emergency setting with psychotic symptoms determined by the Structured Clinical Interview for DSM-IV, positive rather than negative psychotic symptoms predominated with all participants reporting persecutory delusions, and most having delusions of reference and some form of hallucinations (Harris and Batki 2000). While these studies are useful in characterizing substance use-related psychosis, as will be discussed later in relation to METH, utilizing duration of psychotic symptoms as a key determinant in distinguishing primary psychosis from substance-induced psychosis may not be valid in all clinical settings.

MAP has been most consistently described in Japanese populations typically associated with longstanding METH use and characterized as resembling paranoid schizophrenia. Attempting to distinguish psychiatric disease symptoms that are appropriate to the situations within which METH users typically find themselves (purchasing, using, distributing and/or manufacturing the drug or engaging in other illegal activities), those symptoms which are unmasked by METH use but are related to an underlying psychotic illness (e.g., schizophrenia), and those symptoms which are secondary to the drug itself can be challenging. Nevertheless, a subset of METH users develops frank psychotic symptoms across a range from mild paranoia to hallucinations or unusual thought content.

In previous studies of METH users, Japanese, Taiwanese, Australian, and U.S. investigators have identified factors associated with MAP. In early Japanese studies (published 1955–1992), longer duration and more frequent METH use were associated with MAP (Ujike and Sato 2004). Of note, during this time period, Japanese METH users typically used METH exclusively in contrast to the poly-drug use seen in typical U.S. METH users (Ujike and Sato 2004). In 2003, Chen characterized three groups of Taiwanese METH users who were either hospitalized or in a detention center: those with no history of any psychotic symptoms, those with brief psychosis (less than 1 month after last METH use), and those with prolonged psychosis (psychosis which persisted more than 1 month after last METH use). In this study, those with MAP had earlier first METH use and used larger amounts of METH than those who had no history of psychotic symptoms. There was no difference in duration of METH use between the psychosis and non-psychosis group. There were, however, significant pre-morbid schizoid/schizotypal personality trait scores in those with METH-associated psychosis, and there was a significant linear correlation between these trait scores and presence and duration of psychosis. Additionally, the psychosis group had greater alcohol dependence, anti-social personality disorder (ASPD), and major depression (MDD) (Chen et al. 2003). In the same population, the first-degree relatives of those with psychosis were more likely to have schizophrenia than those METH users who had never had psychosis (OR = 5.4, 95% CI: 2.0–14.7, $p < 0.001$). Further, the risk for schizophrenia in the first degree relatives of those with prolonged psychosis was greater than those METH users with brief psychosis (OR = 2.8, 95% CI: 1.0–8.0, $p = 0.042$). Chen noted that the greater the "familial loading for schizophrenia, the more likely a METH user is to develop psychosis and the longer that psychosis is likely to last" (Chen et al. 2005).

In an Australian study of community METH users, McKetin found that MAP typically occurred in the context of METH abuse or dependence rather than "recreational" METH use. In METH users with no prior history of psychosis, the prevalence of psychosis among dependent users was 27% as compared to 8% in non-dependent users. However, daily METH use, injection use, and socio-demographic factors were not associated with METH psychosis (McKetin et al. 2006). In Japanese and Australian studies, method of METH administration (injection versus smoking) did not affect frequency of psychosis (Matsumoto et al. 2002; McKetin et al. 2008). In a study of adults with METH dependence in SUD treatment in the U.S., sexual abuse, greater frequency of recent METH use, and METH use combined with other drug use were associated with psychotic symptoms (Christian et al. 2007). In another U.S. study ($N = 39$) of persons with METH dependence who reported either frequent or infrequent psychosis while intoxicated on METH, there was no difference between the two groups in

measures of intelligence, education, age of first METH use, or duration of METH use. However, those with frequent psychosis reported greater childhood attention deficit disorder (ADHD) and family history of psychiatric illness. Of the participants who had a positive family history for psychiatric illness, 67% had frequent psychotic episodes (Salo et al. 2008). In a small U.S. study ($N = 19$) of individuals being seen in an emergency setting, higher quantitative plasma METH and amphetamine levels were associated with more severe psychotic symptoms, but not to reported amounts of METH ingestion (Batki and Harris 2004). These studies did not identify factors which were consistently associated with MAP. However, the variability in the populations studied (e.g. community v. hospitalized), methamphetamine severity (use v. dependence) or use histories (single drug v. poly-drug) may have contributed to this inconsistency.

While METH psychosis has been discussed in the medical literature since the 1950s, previous studies examining the frequency of MAP have employed varying definitions of the disorder. Additionally, not all of the studies used standardized instruments to measure psychotic symptoms or described the time period (e.g., lifetime, current) within which psychosis was examined. Further, many of these studies (written in Japanese) are not accessible to all investigators. However, in a summary article, Sato noted that in previous Japanese studies more than 76% of METH users had a “paranoid psychotic state with hallucinations” (Sato 1992). In a comparison of non-treatment seeking cocaine- and METH-dependent men and women, METH-dependent individuals were more likely to report psychotic symptoms than cocaine-dependent men and women (Mahoney et al. 2008). While noting the above limitations in definition and diagnosis, as well as the variety of populations studied, in recent studies between 26 and 46% of persons with METH dependence have MAP (see Table 1).

Table 1

Frequency of METH associated psychosis

Population studied	Time period	% Psychotic symptoms	Psychosis definition	Reference
US gay & bisexual treatment-seeking METH abuse/dependent men 18–65 years	Lifetime	26.5%	SCID	Shoptaw et al. 2003
Australian community METH users >16 years	Past Year	13%	BPRS	McKetin et al. 2006
METH dependent		27%		
Non-METH dependent		8%		
Taiwanese incarcerated adolescent METH users	Past Year	7.5%	K-SADS-E	Yen and Chong 2006
U.S. adults in treatment for METH dependence	Lifetime	36%	MINI	Grant et al. 2007
Rural		45%		
Urban		29%		
US METH dependent adults in treatment (didn't distinguish between METH-induced or primary psychotic disorders)	Past or current	12.9%	MINI	Glasner-Edwards et al. 2008
Rural Australian community volunteers >16 years with METH dependence	Lifetime	46%	Self-reported	Wallace et al. 2009
U.S. community and in-treatment METH dependence	Lifetime	45%	MEQ	Leamon et al. 2010

BPRS Brief psychiatric rating scale; *K-SADS-E* Kiddie epidemiologic version of schedule for affective disorders and schizophrenia; *MEQ* METHamphetamine experience questionnaire

MINI Mini-International neuropsychiatric interview; *SCID* Structured clinical inventory for DSM-IV

Signs and symptoms of MAP

While it has been difficult to identify factors consistently associated with MAP or to precisely determine the frequency of MAP, the characterization of MAP symptoms across populations has been quite consistent. Multiple studies in Japanese (Akiyama 2006), Taiwanese (Chen et al. 2003), Australian (McKetin et al. 2006), and Thai (Srisurapanont et al. 2003) populations have described with remarkable consistency a high frequency of persecutory delusions and auditory hallucinations in persons with METH-related psychosis. Other frequently reported symptoms were delusions of reference, visual hallucinations, and thought broadcasting (Chen et al. 2003; Srisurapanont et al. 2003; Akiyama 2006). Ujike and Sato contend that there is a progression of MAP with an initial phase of psychotomimetic effects such as stimulation and heightened concentration, followed by "prepsychosis" with delusions, which may then progress to frank psychosis with hallucinations and delusions of

reference (Ujike and Sato 2004). In a study of 149 METH users, the average latency from first use of METH to onset of psychosis was 5.2 years (Ujike and Sato 2004), while a study comparing METH smokers and METH injectors found a latency of 1.7 years in smokers and 4.4 years in injectors (Matsumoto et al. 2002). Severity of psychotic symptoms has been associated with frequency of METH use, METH injection (Zweben et al. 2004), and severity of METH craving (Nakama et al. 2008).

Most episodes of substance-induced and MAP are of brief duration and resolve as substance levels diminish. However, Japanese investigators have reported that while MAP may be transient with recovery within 1 month of last METH use, METH psychosis may also be prolonged, persisting for longer than 6 months (Ujike and Sato 2004), and may persist despite drug abstinence (Akiyama 2006). Western investigators have been more hesitant to attribute persistent psychotic symptoms solely to substance use and this is reflected in the diagnostic lexicon of the Diagnostic and Statistical Manual-IV which defines substance-induced psychosis as persisting for 1 month or less after last substance use (APA 2000). In contrast, in a Japanese study of 104 hospitalized METH users with no prior history of non-METH-related psychosis, 52% of participants' psychotic symptoms abated within 1 week; whereas, in 26% of participants symptoms persisted for more than 1 month and in 16% of participants symptoms persisted for more than 3 months. Symptoms of psychosis were similar between the transient (duration < 1 week) and persistent (duration > 3 months) groups except that persons with persistent psychosis reported greater non-auditory and non-visual hallucinations (Iwanami et al. 1994). In a Taiwanese study of 174 METH users with psychotic symptoms, 17% had psychosis despite being abstinent for more than 1 month (Chen et al. 2003). In both studies, study participants were abstinent and had no history of schizophrenia or prior psychoses. It is unclear if long duration of MAP reflects the drug's ability to cause a chronic psychotic disorder or if METH is unmasking a psychotic disorder in persons with an underlying psychotic diathesis. As previously noted, chronic psychotic symptoms associated with METH are more likely to occur in those with a family history of schizophrenia or in persons with a premorbid schizoid/schizotypal personality (Chen et al. 2003, 2005). Additionally, a previous neurological disorder (head injury, ADHD, prematurity, learning disability) may increase the risk of treatment-resistant psychosis in METH users (Fujii 2002).

Individuals with a brief METH-related psychosis may relapse to MAP with resumption of METH use or with a stressor such as severe insomnia or heavy alcohol use without METH consumption (Sato 1992; Yui et al. 2000; Ujike and Sato 2004). When MAP recurred with re-exposure to METH the symptoms were nearly identical to those in previous psychotic episodes (Sato 1992). If relapse to psychosis follows METH use, it typically occurs promptly with 60% of METH users relapsing in less than 1 week and 80% relapsing within 1 month. Spontaneous relapse usually occurred in persons with greater than 2 years of METH abuse and vulnerability to relapse provoked by re-use of METH persists for years (Ujike and Sato 2004).

Treatment of MAP

In multiple prior studies, the presence of both psychiatric illness and substance use worsened SUD treatment outcome (Rounsaville et al. 1991; Moos et al. 1994; Weisner et al. 2000). In a study of 526 METH dependent adults, individuals with any history of psychotic disorder at the 3-year follow-up were more than twice as likely to have been hospitalized in the previous 12 months, had more total hospitalizations, had greater severity of their psychiatric symptoms, and were more likely to have attempted suicide than participants with no history of psychosis. However, the two groups did not differ in their duration of SUD treatment attendance, treatment retention, or METH use. This study, however, did not distinguish between primary and substance-induced psychosis and those who required hospitalization were not eligible for study enrollment (Glasner-Edwards et al. 2008). Also of note, in a study of paranoia in community and in-treatment METH users, 37% of those persons with paranoia

obtained a weapon, 11% used a weapon, and 15% attacked another person (Leamon et al. 2010). Only one randomized controlled trial evaluated anti-psychotics in persons with amphetamine-related psychosis. In this 4-week study, there was no significant difference in clinical efficacy between olanzapine and haloperidol (Leelahanaj et al. 2005).

Needs in clinical research

Studies of risk factors for MAP have largely been done in Japanese, Taiwanese, and Australian populations. It is unknown if findings from these large studies are generalizable to other populations such as those in the U.S. given the likely differences in use patterns, socio-environmental factors, and genetics. A single large study of U.S. METH users examined abuse and METH use characteristics and their association with psychosis. However, there are no studies of factors such as perceived stress or cultural stress which have been identified in other populations as being factors in the development of psychoses. Similarly, there are no studies of any kind assessing protective factors for MAP, which may mitigate against risk factors. Of note, none of the above studies examined sleep deprivation as a factor in the genesis of MAP, a factor that is well-described as a stressor which can result in psychosis. Additionally, there are no studies examining what role preexisting conditions, socio-environmental stressors or protective factors play in the severity, persistence or relapse of MAP. Lastly, little is known about the prevention of persistent and recurrent MAP.

Susceptibility genes

MAP is likely a complex genetic disease in which environmental factors interact with multiple polymorphic genes to influence susceptibility. Several studies have reported associations between MAP and genetic variation, including single nucleotide polymorphisms (SNPs), variable number tandem repeats (VNTRs), and insertion/deletions (I/D) (see Table 2). The candidate genes listed in Table 2 were selected based on a wide range of evidence, such as biological function, differential expression in disease, involvement in schizophrenia, which is considered pharmacologically similar to MAP, and findings from animal models. In these studies, allele frequencies were compared in unaffected and affected individuals. Unaffected individuals were generally healthy individuals without a history of psychosis-related disorders. Affected individuals were diagnosed using the ICD-10 or the DSM-IV criteria and were primarily individuals with METH dependence and psychosis (20% of studies reported individuals with METH abuse and psychosis). Of note, several studies consisted of heterogeneous populations that included individuals with and without psychosis. (These populations are annotated as such in Table 2.) Another phenotype often considered in these studies was the clinical course of MAP. The prognosis of MAP varied among individuals, some of whom showed continued psychotic symptoms, even after METH was discontinued. Accordingly, the individuals were categorized based on the duration of the psychotic state after METH discontinuation. Transient psychosis was defined as symptoms that improved within 1 month of METH discontinuation and the start of treatment with neuroleptics; whereas, the prolonged type was defined as psychotic symptoms continuing for more than 1 month after METH discontinuation and the treatment of neuroleptics. The hypothesis-driven studies investigating putative candidate genes and their association with psychosis among METH-dependent individuals are summarized in Table 2. Recognizing the high probability of false-positive associations due to multiple comparisons, we chose to focus on candidate genes with significant associations, i.e., p *value* < 0.001. There were seven genes in this category: D-amino acid oxidase activator, Dystrobrevin-Binding Protein 1, Frizzled 3, Metabotropic Glutamate Receptor 2, 5-Hydroxytryptamine (serotonin) Receptor 1A, Prokineticin Receptor 2, and Glycine Transporter 1.

Table 2

Susceptibility genes associated with METH psychosis

Gene Variant	Ethnicity	Comparison Groups (n)		Genotype (%)			Genotype (%)			*p*-valu
		A	B	A			B			
				M/M	M/m	m/m	M/M	M/m	m/m	
AKT1										
rs3803300	JPT DSM	METHA-Psychosis (182)b	Healthy (437)	34.6	50.0	15.4	28.4	53.5	18.1	0.15
rs1130214	JPT DSM	METHA-Psychosis (182)b	Healthy (437)	70.3	28.0	1.6	72.0	24.7	3.2	0.97
rs3730358	JPT DSM	METHA-Psychosis (182)b	Healthy (437)	74.7	23.6	1.6	83.3	15.6	1.1	0.01
rs2498799	JPT DSM	METHA-Psychosis (182)b	Healthy (437)	22.0	53.8	24.0	27.7	48.3	24.0	0.81
rs2494732	JPT DSM	METHA-Psychosis (182)b	Healthy (437)	47.3	43.4	9.3	48.5	44.0	7.6	0.59
rs2498804	JPT DSM	METHA-Psychosis (182)b	Healthy (437)	34.6	50.5	14.8	32.5	47.1	20.4	0.20
ARRB2										
rs1045280	JPT ICD	METHD-Psychosis (177)a	Healthy (546)	66.1	30.5	3.4	76.4	22.3	1.3	0.01
rs2036657	JPT ICD	METHD-Psychosis (177)a	Healthy (546)	72.9	24.9	2.2	79.9	18.9	1.2	0.11
rs4790694	JPT ICD	METHD-Psychosis (177)a	Healthy (546)	78.0	22.0	0.0	86.0	13.6	0.4	0.01

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Definitions: *METH* methamphetamine; *CHB* Chinese; *JPT* Japanese; *DSM-IV or ICD* Diagnostic criteria for METH dependence/abuse/psychosis, *METHD-Psychosis* METH-dependent individual with psychosis; *METHD-Psychosis/T* METH-dependent individual with transient psychosis that improved within 1 month after discontinuance of METH; *METHD-Psychosis/P* METH-dependent individual with prolonged psychosis lasting greater than 1 month after discontinuance of METH; *METHA* METH abuser; *METHA-Psychosis* METH abuser with psychosis; *NS* No significant differences were detected; *M* Major allele; *m* Minor allele.

[a]Population was composed of METH-dependent individuals with and without psychosis

[b]Population was composed of METH-abusers with and without psychosis

[c]Haplotype analysis resulted in p values < 0.005

D-amino acid oxidase activator (DAOA) DAOA is the gene encoding the d-amino acid oxidase activator. DAOA is expressed in multiple tissues including the amygdala, caudate nucleus, spinal cord and testes (Chumakov et al. 2002). Although the functional mechanisms of DAOA are not fully understood, DAOA activates D-amino acid oxidase, which oxidizes d-serine, an endogenous ligand for the glycine site of the N-Methyl-D-aspartate (NMDA) type glutamate receptor (Chumakov et al. 2002). D-serine levels are low in schizophrenic patients and administration of D-serine has been shown to reduce some of the symptoms of this disease (Kantrowitz et al. 2010). This provides a potential link between DAOA and the glutamate hypo-function hypothesis of schizophrenia, which integrates environmental influences and causative genes, is based on clinical and neuropathological evidence of the hypo-function of glutamatergic signaling via NMDA receptors. The DAOA gene is located on chromosome 13q and has been found to be a susceptibility locus for schizophrenia (Badner and Gershon 2002), and many studies have found an association between genetic variants in DAOA and schizophrenia (Chumakov et al. 2002; Schumacher et al. 2004; Yue et al. 2007). In a case-controlled study, Kotaka et al. (2009) demonstrated an association between a DAOA polymorphism (rs778293; $p = 0.0002$) and psychosis among METH-dependent subjects. This polymorphism was previously shown to be associated with schizophrenia; however, its functionality is unknown.

Dystrobrevin-binding protein 1 (DTNBP1) DTNBP1 encodes dystrobrevin-binding protein 1 also referred to as dysbindin. This ubiquitously expressed, coiled-coil-containing protein is a subunit of the biogenesis of lysosome-related organelles complex 1 (BLOC-1), which regulates trafficking to lysosome-related organelles (Li et al. 2003). In muscle and non-muscle cells, DTNBP1 binds to α- and β-dystrobrevins, components of the dystrophin-associated protein complex (DPC) (Benson et al. 2001). In muscle, the DPC is required for the maintenance of muscle integrity and normal muscle function. In the brain, dysbindin is most prevalent in axons, particularly those with large synaptic terminals such as the mossy fiber synaptic terminals in the cerebellum and hippocampus (Benson et al. 2001). In a case controlled study, Kishimoto et al. (2008a) demonstrated an association of a polymorphism in the DTNBP1 gene and psychosis among METH-dependent individuals (rs3213207; $p = 0.000025$). Furthermore, two haplotypes at these loci were also significantly associated with MAP (*p values* < 0.0015). Significant associations between schizophrenia and DTNBP1 also have been reported (Edwards et al. 2008; Straub et al. 2002). Consistent with this, reduced levels of dysbindin expression have been associated with the pathogenesis of schizophrenia (Talbot et al. 2004; Weickert et al. 2008) and thought to be related to glutamatergic neurotransmission. In schizophrenic patients, dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampus which is inversely correlated with increased vesicular glutamate transporter (Talbot et al. 2004). As evidence is mounting that glutamate hypo-function may be related to the etiology of schizophrenia (Konradi and Heckers 2003), it is postulated that DTNBP1 variants may contribute to MAP through pathways involving glutamatergic neurotransmission. Despite the many genetic studies of this gene, the link between functionality of these polymorphisms and dysbindin expression has not been investigated.

Frizzled 3 (FZD3) Frizzled proteins are cell surface receptors for secreted Wnt proteins (Wang et al. 2006a). Both frizzled and Wnt proteins are thought to be important in central nervous system (CNS) development. FZD3, the human Frizzled-3 gene, is widely expressed in the developing nervous system and is involved in axonal growth and guidance (Wang et al. 2006b). Wnt signaling plays a role in axonal remodeling and synaptic differentiation in the cerebellum (Cadet and Krasnova 2009; Lucas and Salinas 1997) and abnormal Wnt signaling has been linked to schizophrenia (Cotter et al. 1998). FZD3 maps to chromosome 8p21 and consists of eight exons. The 8p22-21 region has been identified as a susceptibility locus for schizophrenia in several studies (Blouin et al. 1998; Gurling et al. 2001; Pulver et al. 1995). However, genetic studies with the Frizzled-3 gene and schizophrenia have been contradictory, with both positive and negative associations among Han Chinese (Yang et al. 2003),

Japanese (Zhang et al. 2004), and Korean (Jeong et al. 2006) populations. Interestingly, the association between Frizzled-3 and MAP has only been observed with haplotypes ($p < 0.00002$) and not at the individual loci, which may indicate a required synergism between the polymorphisms for a phenotypic effect (Kishimoto et al. 2008b).

Metabotropic glutamate receptor 2 (GRM2) GRM2 is another gene involved in glutamatergic neurotransmission and found to be significantly associated with MAP (Tsunoka et al. 2010). *GRM2* is located on chromosome 3p in a region linked to schizophrenia in several studies (Badner and Gershon 2002; Pulver et al. 1995). GRM2 encodes the group II metabotropic glutamate receptor 2 (mGlu2). mGlu2 is a G-protein coupled receptor involved in inhibition of adenylate cyclase and cAMP formation (Cartmell et al. 1999) and the major presynaptic group II autoreceptor activated by synaptically released glutamate (Kew et al. 2002). Although another group II metabotropic glutamate receptor, glutamate receptor 3 (mGlu3), has been implicated in etiological, pathophysiological and pharmacotherapeutic aspects of schizophrenia (Harrison et al. 2008; Lyon et al. 2008; Sartorius et al. 2008), no statistically significant association with *GRM2* and schizophrenia was found in the Japanese population (Joo et al. 2001).

5-Hydroxytryptamine (Serotonin) receptor 1A (5-HT1A) 5-HT1A, the gene encoding the 5-HT receptor 1A, is a G protein-coupled receptor which is widely expressed in the brain, including in the hypothalamus, hippocampus, and cortex. Through serotonin (5-HT) binding, this receptor mediates inhibitory neurotransmission. The serotonin system has been shown to be important in the neural processing of anxiety and the neurobiological control of learning and memory. Similar to the glutamatergic pathway, altered serotonergic neurotransmission is speculated to contribute to schizophrenia susceptibility. Evidence suggests that METH, which acts as a substrate for the 5-HT transporter, elevates extracellular 5-HT levels by both promoting the efflux via transporter-mediated exchange and by increasing cytoplasmic levels by disrupting storage of 5-HT in vesicles (Cadet and Krasnova 2009; Rothman and Baumann 2003). Although studies have explored whether there is an association between several of the genes involved in 5-HT regulation and MAP, only the rs878567 polymorphism in the 5-HT1A receptor was significantly associated using an alpha level of 0.001 as significant (Kishi et al. 2010). Polymorphisms in the 5-HT1A receptor have been associated with schizophrenia in several studies (Huang et al. 2004; Le Francois et al. 2008; Lemonde et al. 2003, 2004), including the rs878567 polymorphism. Currently, 5-HT(1A) receptor agonists are being considered for the treatment of schizophrenia (McCreary and Jones 2010).

Prokineticin receptor 2 (PROKR2) PROKR2 encodes prokineticin receptor 2 (PK-R2), an integral membrane G-protein coupled receptor for prokineticins. Prokineticins and their receptors are involved in a wide range of biological functions in multiple organ systems. In the CNS, prokineticin 2 modulates neurogenesis, circadian rhythms, and migration of the subventricular zone-derived neuronal progenitors (Cheng et al. 2002; Ng et al. 2005). The involvement of PK-R2 in circadian rhythm raises the question of whether this gene may be associated with mood disorders, a phenotype often observed in patients with drug addiction. Several animal studies have shown that METH increases expression of circadian genes in the brain (Iijima et al. 2002). The PROKR2 gene is located on chromosome 20p12.3, which was shown to be linked to bipolar disorder in three studies (Detera-Wadleigh et al. 1997; Fanous et al. 2008; Ross et al. 2008). An association between PROKR2 gene variants and major depressive disorder and bipolar disorder was reported in a Japanese population (Kishi et al. 2009b); however, this study was small and confirmatory studies will be necessary to validate this finding. Furthermore, these same investigators have shown that 3 individual SNPs in the PROKR2 gene (rs6085086, rs4815787, rs3746682), as well their haplotypes ($p \leq 0.00019$), were associated with MAP (Kishi et al. 2010).

Glycine transporter 1 (SLC6A9) SLC6A9, which encodes the glycine transporter type 1 (GLYT1), is involved in glutamatergic neurotransmission, particularly at NMDA-type glutamate receptors. It is currently believed that termination of the different synaptic actions of glycine is produced by rapid re-

uptake through two sodium- and chloride-coupled transporters, GLYT1 (located in the plasma membrane of glial cells) and GLYT2 (located in pre-synaptic terminals). GLYT1 regulates both glycinergic and glutamatergic neurotransmission by controlling the reuptake of glycine at synapses. The NMDA receptors are regulated in vivo by the amino acids glycine and D-serine. Glycine levels, in turn, are regulated by GLYT1, which serves to maintain low sub-saturating glycine levels in the vicinity of the NMDA receptors. Competitive antagonists of NMDA receptors produce a psychotic state in healthy subjects and exacerbate symptoms in schizophrenics. SLC6A9 has emerged as a key novel target for the treatment of schizophrenia. Morita et al. examined SLC6A9 among Japanese subjects with METH-dependence and psychosis (Morita et al. 2008). Two SNPs conferred an increased risk for MAP (rs2486001 and rs2248829) in addition to the haplotype T-G ($p = 0.000037$). It is speculated that variants of the SLC6A9 gene may affect susceptibility to MAP by modulating NMDA receptor function.In summary, there is reasonably strong evidence that genetic variation in neurotransmitter systems and in neural development or growth is associated with risk for MAP. Of the seven genes with strong empirical support for association with MAP, four are involved in glutamatergic neurotransmission (DAOA, DTNBP1, GRM2 and SLC6A9). Potential epistatic (i.e. gene x gene) interactions among these glutamatergic genes should be investigated. Polymorphism in a key gene in serotonin system regulation and signaling (HTR1A) is also associated with risk for MAP, which suggests that other 5-HT system genes may also be good candidates. Finally, two genes with roles in CNS development (FZD3) and neurogenesis (PROKR2) may help to identify other genes as well as developmental processes that mediate vulnerability to MAP.

Gaps in genetic research

These studies reviewed in relation to MAP have examined candidate genes selected based on current concepts of neurobiology. Priorities for future genetic research on MAP include: replicate genetic associations within and across ethnically diverse populations; adjust for multiple comparisons to minimize false-positive associations; utilize linkage disequilibrium and tagSNP information to capture the polymorphic structure of candidate genes; increase statistical power by using larger population cohorts to minimize false-negative associations; improve phenotyping of MAP by use of a continuum versus a categorical classification and account for trajectory of cessation, treatment response and relapse; identification of allele-specific in vivo activity in humans and non-human animals.

METH neuropathobiology

Lines of evidence support the notion that METH abuse leads to neurodegeneration and, as such, may be a component part of MAP pathobiology (Krasnova and Cadet 2009). The neuropsychological events noted show deficits in attention, working memory, and decision making in METH addicts. Bioimaging and histopathologic evaluations show that the clinical findings parallel composite damage to dopamine and serotonin axons, loss of gray matter with linked hypertrophy of the white matter and microgliosis in different brain areas (Kuhn et al. 2008; Thomas et al. 2004a, b, 2008a, b; Xu et al. 2005). The molecular basis of such neurotoxicities, interestingly, parallel neural damage seen in a range of neurodegenerative disorders that include Alzheimer's and Parkinson's disease, HIV-associated neurocognitive disorders, and amyotrophic lateral sclerosis. Such neurotoxicity and inevitable neurodegeneration parallels the presence of oxidative stress, excitotoxicity, neuroinflammation, mitochondrial dysfunction, decreased antioxidants and stress patterns (Cadet and Krasnova 2009). These effects a host of intracellular organelle functions and suggests that a range of therapeutic strategies can be developed that would slow or reverse adverse neuronal events (Kosloski et al. 2010; Mosley and Gendelman 2010; Stone et al. 2009).

Animal models

In this section, we review the published preclinical animal research that aims to simulate or directly understand some facet of METH-related psychosis. We will not attempt to survey the vast literature on neurobiologic and neurotoxic effects of METH exposure as it is beyond the scope and the focus of the present paper. The interested reader is referred to the following reviews on these topics (Cadet and Krasnova 2009; Fleckenstein et al. 2007; Volz et al. 2007). This section of the review, however, will have an eye toward the validity of the animal models that have been used to date, as well as identifying key gaps in the methods and research that need to be filled. Given the paucity of animal research directly focused on questions related to MAP, an important goal of this section is to make recommendations for future research that involves the development of translationally-relevant models that are reliable (i.e., reproducible) and predictive (Geyer and Markou 1995).

Clearly, establishing animal models that are predictive of the human phenomenon of interest (MAP in this case) will not happen without experimental situations and associated manipulations that are reproducible and consistent within and across laboratories. We agree with writers that espouse the best way to this broad form of predictive validity and to strong translational animal models is to work toward improving construct and etiological validity (Geyer and Markou 1995; Markou et al. 2009). For construct validity, attention to continually improving the match between what is measured at the behavioral (psychological) and neural levels in the animal models of MAP with what is believed to be the behavioral and neural processes underlying this psychosis in humans (Markou et al. 2009) is essential. As an example, if the current state of knowledge suggests that individuals with MAP have impaired sensorimotor gating that leads to sensory flooding and cognitive fragmentation, then some insight regarding the human condition may come from a better understanding of a similar attentional process in animal models. In this example, pre-pulse inhibition (PPI) may be of particular import. Pre-pulse inhibition refers to the decrease in startle response evoked by an auditory stimulus that is preceded by a pre-pulse stimulus (usually the startle stimulus at lower intensity and shorter duration). Deficits in PPI inhibition have been reported in patients diagnosed with schizophrenia, as well as in rats pretreated with METH (Abekawa et al. 2008) or have a history of self-administering METH (Hadamitzky et al. 2011; see later).

The strategy of searching for and establishing construct validity likely means that no single animal model will be sufficient to capture all processes relevant to the disorder of interest in humans. Also, this strategy is inherently translational. Working toward etiologic validity further encourages the communication and sharing of ideas, theories, and methods necessary for successful translational research (Markou et al. 2009). Etiologic validity refers to the matching of environmental and physiological precursors presumably responsible for the onset of the disorder. There is ongoing debate as to the extent that METH induces psychotic symptoms versus exacerbating pre-existing symptoms (see earlier). This is one of many unique instances in which animal models could serve to inform this important clinical issue. For instance, will rats intravenously self-administer enough METH to alter those behavioral and neural processes altered in humans diagnosed with MAP? Are the predisposing factors, whether environmental, neural, or genetic, thought to be relevant in human MAP contributing to such effects in the animal models? Prior research has demonstrated that under some conditions rats self-administering METH will show deficits in object recognition memory (Reichel et al. 2011) and PPI (Hadamitzky et al. 2011). Unfortunately, this research is quite limited within the context of greater understanding of MAP in humans. Given that METH psychosis is associated with severe behavioral and neuropsychiatric complications (see earlier), there is a pressing need to definitively and precisely identify the behavioral and neurobiological mechanisms underlying the development of METH psychosis. As a result of this identification, behavioral interventions and psychopharmacological treatment strategies can then be developed.

Despite the limited work, animal studies have consistently shown that many psychological processes underlying clinical features of METH psychosis can be reproduced in a variety of animal species, including mice, rats, guinea pigs, cats and non-human primates (e.g., Japanese monkeys). Like METH addicts, animals that are chronically treated with a low (non-toxic) dose of METH gradually develop psychotic-like symptoms, such as a decrease in motor activity, an increase in stereotypies, decreased interest to external stimuli and surroundings, and decreased social functioning (Kuczenski et al. 2009). Also, some of the changed behavioral patterns (e.g., behavioral sensitization) persist even long after the cessation of drug treatment, and have a tendency to relapse or exacerbation upon re-exposure to the drug. Furthermore, concurrent antipsychotic drug treatment can prevent recurrence triggered by METH use (Misra et al. 2000). These results strongly suggests that animal models of METH psychosis have high face (e.g., similarities to clinical symptoms), construct (e.g., METH use and associated brain changes), and predictive validity (e.g., antipsychotic effect), and are effective in reproducing behavioral symptoms of human METH psychosis, mimicking the time course of symptom development, and its liability to exacerbation.

Behavioral characteristics of MAP in nonhuman primates Most of this work has been carried out by Japanese researchers since the early 1970s beginning during the decade immediately after World War II when METH abuse occurred in epidemic proportions in Japan (Ujike and Sato 2004). Japanese psychiatrists had observed an increased number of cases of MAP in chronic METH users and began to investigate the behavioral characteristics of the psychosis and associated biochemical mechanisms in animals. Nonhuman primate models are thought to be better than other species models in capturing complex and fine-grained behavioral abnormalities resembling human MAP, especially aspects of perceptual aberrations, social interaction, and interpersonal relationship. This is because monkeys, especially Japanese monkeys (*Macaca fuscata*) are well known to form a stable and intricate hierarchical society in which each member follows a certain rank order appropriate in interacting with others.An early study provided a vivid description of acute and chronic effects of METH treatment on a group of Japanese monkeys (Machiyama 1992). They gave monkeys intramuscular METH injection at 1.0 mg/kg from Monday to Saturday for 3–6 months. At the same time, physiological saline was given by intramuscular injection to the other animals that served as controls. Upon acute treatment, some monkeys showed motor excitation, whereas other showed motor suppression. They identified that this marked individual difference was due to the different behavioral traits of monkeys in the group. Active monkeys that showed enhanced repetitive motor activity to acute METH were those aggressive individuals occupying higher ranks while non-active monkeys, at the bottom in the ranking order, demonstrated a decrease in motor activity to acute METH treatment. Over the course of repeated drug treatment, some monkeys developed behavioral abnormalities in a variety of psychological domains. In the *sensorimotor* domain, after about 1 month treatment, some monkeys displayed a stereotypical body-fingering behavior which entailed continuous fingering and investigating certain parts of the body, such as the wrist, thigh, abdomen, penis, or scrotum (Machiyama 1992). In the *perception* domain, after about 2 months of repeated treatment, some monkey displayed hallucination-like perceptual distortions (e.g., “staring” at vacant space, floor or certain body parts of their own or cage mates, and at times touching with fingers). In the *social behavior* domain, some monkeys gradually lost interest in social interaction (e.g., grooming and mounting), and withdrew to stay in a location in the cage, and could suddenly show inexplicable aggression and fear, and broken behavioral response patterns (termed “splitting”). There were also marked individual differences. Monkeys, with middle and high ranks that responded actively to acute METH injection, demonstrated the most severe behavioral abnormalities in response to chronic METH treatment. Monkeys with lower ranks fared better and only exhibited mild changes. Two high ranked monkeys even died before the entire experiment was completed. After the termination of daily injections, some behavioral abnormalities disappeared, while others persisted for an extended period. In general, perceptual aberrations (e.g., staring, fixation) diminished rather rapidly and to a greater extent than deficits in sensorimotor (e.g.,

fixating) and social functioning (e.g., social withdrawal). Also, some monkeys who exhibited persistent behavioral changes that were easily identifiable by uninformed observers recovered better than others. Most interestingly, the psychotic behaviors of chronically treated monkeys could be re-triggered by a saline injection or a METH injection, mimicking clinical phenomena of stress and drug priming-induced relapse of METH psychosis.One of the issues with these observational studies is the lack of formal assessments of psychological functions. Therefore, it is unclear what psychological function(s) (e.g., attention, working memory, episodic memory, executive functioning, emotional regulation, etc.) were impaired by chronic METH treatment that contributed to the observed behavioral abnormalities. The second issue is that the experimenter-controlled METH administration regimen did not mimic human METH use (via self-administration) and the constant dosing regimen used in the monkey studies also did not reflect the typical pattern of human METH use. Most METH abusers start with very low doses of the drug and have had a long history of progressively escalating their doses. Thus, human METH psychosis often appears during the course of escalating dosage of drug administration (i.e., “binges” or “runs”), and discontinuation of drug usage usually results in a rapid decline of the psychosis, closely paralleling urine drug levels (Angrist 1994; Davis and Schlemmer 1980; Kuczenski et al. 2009). This aspect of METH use pattern was not mimicked in these early studies.There are several issues that may hinder the effort to delineate the neurobiological underpinnings of METH psychosis. The first is the lack of validated rodent behavioral models of METH psychosis. Unlike non-human primate models, which provide richer behavioral repertoires sensitive to the psychotomimetic effect of METH, most rodent studies focus on motor activity and stereotypy. Behavioral sensitization is taken as signs of METH psychosis (Martinez et al. 2005; Nestler 2001; Robinson and Becker 1986; Segal and Mandell 1974; Segal et al. 1981). One issue with psychomotor sensitization and stereotypy as behavioral indices of METH psychosis is that they do not seem to capture the emotional, cognitive, and perceptual disturbances that characterize human METH psychosis disorders. Other behavioral abnormalities induced by repeated METH treatment, such as disruption of PPI of acoustic startle response, may provide a better model (Braff et al. 2001). The following section discusses this rodent research in more detail.

Behavioral characteristics of METH psychosis in mice and rats To date, the behavioral models explicitly developed for studying symptoms of MAP in rodents fall into three broad categories: i) METH-induced deficits in PPI, ii) METH attenuation of social interactions, and iii) METH induced stereotypy and alterations in locomotion. The following narrative will provide an overview of this research and highlight some key findings that indicate their possible utility for understanding aspects of MAP in humans.

Pre-pulse inhibition (PPI) Rodents will startle to a sudden loud sound such as a 40 ms, 120-dB white noise. Under typical conditions, this startle reaction is reduced if this startle stimulus is preceded by a shorter and less intense pre-pulse stimulus (e.g., 20 ms, 72-dB white noise). This inhibition of the startle is thought to measure sensorimotor gating (Braff and Geyer 1990). Individuals diagnosed with schizophrenia show deficits in PPI; an effect that can be simulated by acute and repeated treatment with METH. For example, Arai and colleagues found that mice pretreated with 3 mg/kg METH showed reduced PPI (Arai et al. 2008). A similar acute METH treatment protocol has been shown to be effective at producing PPI deficits in rats (Maehara et al. 2008). Of note, this deficit in PPI was not seen in mice treated acutely with 1 mg/kg METH (Arai et al. 2008). However, in that same report by Arai et al., repeated treatment with METH (1 mg/kg) for 7 days disrupted PPI and this deficit persisted after 7 days of abstinence from METH. More recently, Hadamitzky et al. (2011) report deficits in PPI in rats that had an extended history of self-administering intravenous METH. This research reflects an important advance in developing a translational model to study aspects of MAP. That is, like humans, this alteration in sensorimotor gating was self-induced by the rat.Behavioral pharmacology research investigating the mechanism of the METH-induced deficits in PPI have focused either on the effects of established antipsychotic medications or on the effects of ligands thought to act on receptor processes

involved in aspects of the psychosis. Along the former lines, the typical antipsychotic medication haloperidol has been shown to alleviate PPI deficits induced by acute treatment with METH (Maehara et al. 2008). Further, the atypical antipsychotics olanzapine and risperidone alleviated PPI deficits induced by repeated METH treatment (Abekawa et al. 2008). Arai and colleagues found that the $GABA_B$ agonist baclofen alleviated deficits in PPI induced by acute and chronic METH exposure (Arai et al. 2009). Further, the cholinergic system appears to be important for METH-induced deficits in PPI. For example, pretreatment with the muscarinic agonist oxotremorine blocked METH-induced deficits in PPI (Maehara et al. 2008). In this same report, the investigators did not find an effect of the nicotinic agonist nicotine. This result contrasts with (Mizoguchi et al. 2009) who found that pretreatment with nicotine alleviated PPI deficits produced by METH. Further, the nicotinic antagonist dihydro-β-erythroidine (DHβE) and METHyllycaconitine both blocked this ameliorative effect of nicotine indicating a role for α4β2- and α7-containing nicotinic acetylcholine receptors. The most notable difference in protocol between these discrepant reports was that Maehara et al. 2008 used rats; whereas, Mizoguchi et al. 2009 used mice. Regardless, the comorbidity between METH and tobacco use, as well as schizophrenia and tobacco use, makes this an important area for future research.

Social interaction When a rat is paired with a conspecific, they show a variety of species-specific behaviors. These behaviors include sniffing, grooming, crawling over or under, and nosing (Barnett 1963). Some researchers have suggested that alternations in social interaction resulting from METH exposure may be a useful model to study the paranoid and social anxiety symptoms of humans with MAP (Clemens et al. 2004; Rawson et al. 2002). Previous research has shown that acute METH treatment can alter social interaction. For example, Shinba et al. 1996 found that rats treated with either 0.1 or 1 mg/kg METH on average spent their time further away from the conspecific in the environment than saline controls [see also (Arakawa 1994)]. Perhaps of more interest from a modeling or simulation perspective is the more recent work by Clemens and colleagues showing 'social withdrawal' in rats following an abstinence period from METH (Clemens et al. 2007a, b). In one study, Clemens and colleagues administered METH at 2.5 or 5 mg/kg every 2 h for a total of 4 injections. METH increased general activity in the chamber across the entire 7.5 h treatment/measurement period regardless of dose (Clemens et al. 2004). Rats treated with the highest dose of METH (20 mg/kg total) also developed head weaving at the end of the treatment period, suggesting stereotypy with this protocol (see next section). Acute high dose METH increased activity and head-weaving. Albeit interesting, the most notable finding from the perspective of this report is that following 4 weeks of abstinence from METH these rats had significantly lower social interaction score than controls. Subsequently, this social withdrawal finding was extended to a treatment regimen in which rats were administered 8 mg/kg METH once per week for 16 weeks (Clemens et al. 2007a, b). In fact, the alterations in social interaction were seen after 7 weeks of abstinence.

Stereotypy and alterations in locomotion As the acute dose of METH increases, its behavioral effect in rats and mice generally shifts from inducing hyperactivity to inducing stereotypy. These effects of METH can become exaggerated (i.e., sensitization) with repeated treatment (Bevins and Peterson 2004; Kuczenski et al. 2009; Maehara et al. 2008; Ujike et al. 1989). Further, a handful of papers published in the 1960s showed that spontaneous wheel running, activity, and reactivity to external stimuli are blunted long after (e.g., 10 weeks) chronic treatment with METH has ceased [see Utena 1961, 1966); Yagi 1963; Yui et al. 2000 and Machiyama 1992 for more detailed discussion of this and related research]. The presentation of such behavioral alterations that sensitize with repeated treatment and persist with abstinence has been considered a model for some of the symptoms of psychosis (Machiyama 1992; Takigawa et al. 1993; Yui et al. 2000). Converging support for this notion comes from the overlap in the neurobiological processes underlying these motor effects of METH and that of psychosis in humans, as well as behavioral pharmacologic work indicating the effectiveness of antipsychotic medications. For instance, METH-induced locomotor stimulation is blocked by clozapine, haloperidol, and chlorpromazine (Maehara et al. 2008; Okuyama et al. 1997). Notably,

METH-induced stereotypy in the work of Okuyama et al. 1997 was blocked by haloperidol and chlorpromazine, but not clozapine. Additional pharmacologic research has implicated the serotonergic, dopaminergic, and muscarinic systems in these effects (Balsara et al. 1979; Maehara et al. 2008; Ujike et al. 1989). For instance, Ujike et al. 1989 found that repeated daily METH treatment in rats (4 mg/kg for 14 days) increased locomotion and stereotypy. Pretreatment with dopamine D1 receptor antagonists SCH23390 or the D2 receptor antagonist YM-09151-2 blocked this sensitization.Most of the repeated or chronic METH exposure research in this area involves a daily injection of METH for a prescribed number of days. Notably, a recent study by Kuczenski et al. (2009) sought to investigate these shifts in locomotor stimulation and stereotypy in rats, using an intravenous infusion protocol designed to more closely mimic the chronic escalating use of METH seen in humans and simulate the longer half-life of METH in humans (ca. 12 h in human versus 1 h in rats). Their findings confirm and extend earlier research describing the development of stereotypy, as well as disruption of sleep, in what seems to be a more translationally relevant model of MAP. Whether this is the case or not will need to await further research. However, one limitation of this model that will need to be overcome, if this model is to be more widely adopted, is the high mortality rate of the rats in the escalating METH exposure phase.

Neurobiological mechanisms underlying MAP

Chronic METH use profoundly changes the brain structures and chemistry (Chang et al. 2007). Studies on the METH-induced brain changes relevant to MAP have focused on the catecholaminergic systems (e.g., dopamine, norepinephrine, 5-HT, etc.). This approach makes sense given that METH is known to cause both acute and chronic neurotoxic changes in dopaminergic and serotonergic neurons in animals and humans and that psychosis in schizophrenia is thought to result from hyperactivity of the mesolimbic dopaminergic system. Some structural changes (enlarged lateral ventricle, enlarged basal ganglia, reduced hippocampal volume), that have been reported in patients with schizophrenia, have also been found in people who were chronic METH users, strongly indicating that these structural changes and their underlying mechanisms may be responsible for METH psychosis (Chang et al. 2007).

Human postmortem and imaging studies have consistently shown that chronic METH use causes a reduction of dopamine transporter (DAT) density in the various dopaminergic systems, including the dorsal striatum, nucleus accumbens, and prefrontal cortex. However, this pronounced effect persists long after cessation of drug administration (Sekine et al. 2001, 2003; Volkow et al. 2001c; Wilson et al. 1996). The striatal dopamine D2 density is generally not affected. However, lower level of D2 receptor availability in the orbitofrontal cortex has been reported (Volkow et al. 2001a). Furthermore, there seem to be a significant negative correlation between the clinical severity of psychotic symptoms and DAT density, and a positive correlation between the duration of METH use and the severity of psychotic symptoms, suggesting that chronic METH use causes the reduction in DAT density, which may directly contribute to the development of METH psychosis (Iyo et al. 2004). Volkow et al. (2001b) also reported that the chronic METH-induced reduction in DAT is associated with motor and cognitive impairment. They found that there was a negative correlation between the DAT reductions and the impaired motor performance, and a positive correlation between the levels of DAT reductions and verbal memory performance: the lower the dopamine (DA) transporter level, the slower the motor responses, and the greater worsening of memory performance. However, because the reduced striatal DAT density tends to recover following METH abstinence (>6 months) (Volkow et al. 2001b) while METH psychosis persists long after the absence of METH use (Sato 1992), the direct and definite link between DAT reduction and METH psychosis is still lacking. It is possible that other permanent neuroadaptions caused by DAT reduction also play a role. Other human studies also reported that during the spontaneous recurrences of METH psychosis (referred to as “flashbacks”), there were

increases in plasma DA and norepinephrine levels (Yui et al. 1999), consistent with the notion that increased DA neurotransmission, coupled with increased noradrenergic hyperactivity (due to stress) may contribute to psychotic symptoms.

In contrast to limited research on human subjects, there are many studies that have examined METH-induced brain changes in rodents. Although many structural and neurochemical changes induced by METH use/abuse has been revealed, whether those changes are directly related to MAP or even contributing to MAP is less certain. To ensure that the neurochemical changes discussed here are potentially relevant to the underpinnings of MAP, in this section, we will narrow our discussion to research that has demonstrated behavioral sensitization following human patterns of METH abuse (e.g., chronic and escalating dose regimens followed by repeated high-dose METH use). Behavioral sensitization refers to a progressive increase in motor and stereotypical responses to repeated drug treatment (Martinez et al. 2005; Nestler 2001; Robinson and Becker 1986). Thus, the acute effect of METH use is not covered here. The rationale behind this approach is that endogenous sensitized dopaminergic function (e.g., progressively enhanced DA supersensitivity) is believed to be the critical cause of MAP (Ujike 2002; Ujike and Sato 2004). Because behavioral sensitization is the direct "readout" of central DA sensitization, it becomes an indispensable proxy measure of MAP. Because clinical observations suggest that MAP (as well as other psychostimulant psychosis) often emerges after repeated high-dose binges or runs, typically preceded by a more intermittent and escalating pattern of METH abuse, animal models that utilize a long-term intermittent and/or escalating dose regimen, followed by repeated high-dose METH runs are most likely to capture the clinical feature of MAP, and afford us the best chance to identify the neurochemical changes accompanied with MAP. Thus, studies utilizing this approach will be emphasized.

Chronic treatment of METH causes an increase of dopaminergic neurotransmission in the striatum. For example, Nishikawa et al. (1983) found that repeated METH treatment (6 mg/kg per day for 3–14 days) produced a robust behavioral sensitization in the form of augmented stereotypy. A later challenge injection of a lower METH dose (2 mg/kg) increased DA turnover (lower DA and higher 3, 4-dihydroxyphenylacetic acid levels, higher ratios of 3, 4-dihydroxyphenylacetic acid over DA) in the striatum and mesolimbic area of the sensitized animals. Kazahaya et al. (1989) also found that a challenge injection of METH after 7 days withdrawal from chronic administration of METH (4 mg/kg for 14 days) markedly increased DA release in the striatum. Segal and Kuczenski (1997) found that multiple short-interval METH injections (four daily injections at 2-hr intervals at 4.42 mg/kg) produced an augmented DA and serotonin release in both the nucleus accumbens and caudate-putamen in rats that were pretreated with METH for 16 days. These findings, coupled with the findings that repeated METH treatment directly sensitizes DA receptors in the nucleus accumbens and ventral tegmental area (Amano et al. 1996, 2003), and reduces striatal DAT (Izquierdo et al. 2010), strongly suggests that the enhanced striatal DA neurotransmission (e.g. increased DA release and supersensitivity of receptors) plays an important role in METH-induced behavioral sensitization. As discussed earlier, pharmacologic evidence is consistent with this finding. Ujike et al. 1989 showed that pretreatment of SCH 23390 (a selective D1 DA receptor antagonist) or YM-09151-2 (a selective D2 DA receptor antagonist) prevented the development of behavioral sensitization induced by repeated METH injection for 14 days and reduced the enhanced DA release produced by METH challenge.

Chronic METH users often take the drug continuously, and the plasma drug concentrations are elevated and maintained throughout a 2–3 day binge. Studies simulating this pattern of human METH use often employ an escalating dose (ED)-multiple binge rodent model (Kuczenski et al. 2009; Segal and Kuczenski 1997, 1999). Kuczenski et al. (2009) developed a computer-controlled, intravenous drug delivery methodology with dynamic infusion which imposes a 12-hour half-life of the drug in rats to

reproduce a plasma METH profile that approximates human METH pharmacokinetics. Using this drug administration procedure, they still found a prolonged elevation in caudate extracellular DA and behavioral sensitization.

In addition to DA, chronic METH use also produces changes in other neurotransmitter systems, which are also implicated in METH-induced behavioral sensitization. For example, it has been shown that repeated METH treatment (3 mg/kg/day for 30–50 days) increased serotonin levels in cats, which were restored by chlorpromazine treatment (Utena 1966). Rats receiving single daily injections of METH, followed by multiple runs (four daily injections at 2-hr intervals) showed a decrease in serotonin response in the striatum during runs (Segal and Kuczenski 1997). The findings that pretreatment with MDL 72222, a 5-HT_3 antagonist, can attenuate both the development and expression of METH-induced behavioral sensitization (Yoo et al. 2006), and repeated treatment with aripiprazole (a drug with 5-HT_{1A} agonist action) during the withdrawal period from repeated METH treatment attenuated METH-induced behavioral sensitization (Futamura et al. 2010), also point to the notion that serotonin-mediated neurotransmission are related to the psychotomimetic effect of METH. Other neurotransmitters implicated in METH sensitization include substance P and sigma receptors, as evidenced by the findings that repeated METH treatment decreased the substance P receptor binding (Ujike et al. 1988) and sigma receptor antagonist BMY 14802 prevents the development of behavioral sensitization induced by repeated administration of METH (Ujike et al. 1992).

Conclusion

There is great need for increased research to further understand factors related to MAP and how this psychosis affects METH use, dependence, and treatment outcomes. The current state of knowledge suggests that these factors, and their interaction, will span genetic to socioenvironmental influences. As such, research directed at the better understanding of MAP, by necessity, will need to be translational. This review identifies some gaps in our understanding and outlined potential future avenues of research that could help realize this goal of better treatment efficacy for METH-dependent individuals with MAP. For instance, there are no studies assessing protective factors for MAP, which may mitigate against risk factors for psychosis. Does level of familial support, as an example, during treatment affect symptom expression and/or treatment outcome? Along these lines, there is a solid foundation of genetics work that has identified several candidate genes that may play a role in MAP development. However, larger studies of more ethnically diverse populations that likely have unique risk and protective factors are needed. Finally, advances in the development of animal models that show etiological and predictive validity are needed for a more complete understanding of the causes of MAP. These models would likely assist in drug development and behavioral interventions.

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References

- Abekawa T, Ito K, Nakagawa S, Nakato Y, Koyama T. Olanzapine and risperidone block a high dose of methamphetamine-induced schizophrenia-like behavioral abnormalities and accompanied apoptosis in the medial prefrontal cortex. Schizophr Res. 2008;101:84–94. [PubMed]

- Akiyama K. Longitudinal clinical course following pharmacological treatment of methamphetamine psychosis which persists after long-term abstinence. Ann New York Acad Sci. 2006;1074:125–134. [PubMed]
- Amano T, Matsubayashi H, Sasa M. Hypersensitivity of nucleus accumbens neurons to methamphetamine and dopamine following repeated administrations of methamphetamine. Ann N Y Acad Sci. 1996;801:136–147. [PubMed]
- Amano T, Matsubayashi H, Seki T, Sasa M, Sakai N. Repeated administration of methamphetamine causes hypersensitivity of D2 receptor in rat ventral tegmental area. Neurosci Lett. 2003;347:89–92. [PubMed]
- Angrist B. Amphetamine psychosis: clinical variations of the syndrome. In: Cho A, Segal D, editors. Amphetamine and its analogues. San Diego: Academic; 1994. pp. 387–414.
- Aoyama N, Takahashi N, Kitaichi K, Ishihara R, Saito S, Maeno N, et al. Association between gene polymorphisms of SLC22A3 and methamphetamine use disorder. Alcohol Clin Exp Res. 2006;30:1644–1649. [PubMed]
- Diagnostic and statistical manual of mental disorders. 4. Washington: American Psychiatric Association; 2000.
- Arai S, Takuma K, Mizoguchi H, Ibi D, Nagai T, Takshashi K, et al. Involvement of pallidotegmental neurons in methamphetamine- and MK-801-induced impairment of prepulse inhibition of the acoustic startle reflex in mice: reversal by GABAB receptor agonist baclofen. Neuropsychopharmacology. 2008;33:3164–3175. [PubMed]
- Arai S, Takuma K, Mizoguchi H, Ibi D, Nagai T, Kamei H, et al. GABAB receptor agonist baclofen improves methamphetamine-induced cognitive deficit in mice. Eur J Pharmacol. 2009;602:101–104. [PubMed]
- Arakawa O. Effects of methamphetamine and methylphenidate on single and paired rat open-field behavior. Physiol Behav. 1994;55:441–446. [PubMed]
- Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry. 2004;184:110–117. [PubMed]
- Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry. 2002;7:405–411. [PubMed]
- Balsara JJ, Jadhav JH, Muley MP, Chandorkar AG. Effects of drugs influencing central serotonergic mechanisms on methamphetamine stereotyped behavior in the rat. Psychopharmacology. 1979;64:303–307. [PubMed]
- Barnett SA. The rat: a study in behaviour. Chicago: Aldine; 1963.
- Batki SL, Harris DS. Quantitative drug levels in stimulant psychosis: relationship to symptom severity, catecholamines and hyperkinesias. Am J Addict. 2004;13:461–470. [PubMed]
- Benson MA, Newey SE, Martin-Rendon E, Hawkes R, Blake DJ. Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. J Biol Chem. 2001;276:24232–24241. [PubMed]
- Bevins RA, Peterson JL. Individual differences in rats' reactivity to novelty and the unconditioned and conditioned locomotor effects of methamphetamine. Pharmacol Biochem Behav. 2004;79:65–74. [PubMed]
- Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, et al. Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat Genet. 1998;20:70–73. [PubMed]
- Braff DL, Geyer MA. Sensorimotor gating and schizophrenia: human and animal model studies. Arch Gen Psychiatry. 1990;47:181–188. [PubMed]
- Braff DL, Geyer MA, Light GA, Sprock J, Perry W, Cadenhead KS, et al. Impact of prepulse characteristics on the detection of sensorimotor gating deficits in schizophrenia. Schizophr Res. 2001;49:171–178. [PubMed]
- Cadet JL, Krasnova IN. Molecular bases of methamphetamine-induced neurodegeneration. Int Rev Neurobiol. 2009;88:101–119. [PubMed]

- Cartmell J, Monn JA, Schoepp DD. The metabotropic glutamate 2/3 receptor agonists LY354740 and LY379268 selectively attenuate phencyclidine versus d-amphetamine motor behaviors in rats. J Pharmacol Exp Ther. 1999;291:161–170. [PubMed]
- Caton CLM, Drake RE, Hasin DS, Domingues B, Shrout PE, Samet S, et al. Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. Arch Gen Psychiatry. 2005;52:137–145. [PubMed]
- Chang L, Alicata D, Ernst T, Volkow N. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. Addiction. 2007;102(Suppl 1):16–32. [PubMed]
- Chen CK, Lin SK, Sham PC, Ball D, Loh EW, Hsiao CC, et al. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. Psychol Med. 2003;33:1407–1414. [PubMed]
- Chen CK, Hu X, Lin SK, Sham PC, Loh EW, Li T, et al. Association analysis of dopamine D2-like receptor genes and methamphetamine abuse. Psychiatr Genet. 2004;14:223–226. [PubMed]
- Chen CK, Lin SK, Sham PC, Ball D, Loh EW, Murray RM. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. Am J Med Genet B Neuropsychiatr Genet. 2005;136:87–91. [PubMed]
- Chen CK, Lin SK, Huang MC, Su LW, Hsiao CC, Chiang YL, et al. Analysis of association of clinical correlates and 5-HTTLPR polymorphism with suicidal behavior among Chinese methamphetamine abusers. Psychiatry Clin Neurosci. 2007;61:479–486. [PubMed]
- Cheng MY, Bullock CM, Li C, Lee AG, Bermak JC, Belluzzi J, et al. Prokineticin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. Nature. 2002;417:405–410. [PubMed]
- Christian DR, Huber A, Brecht M-L, McCann MJ, Marinelli-Casey P, Lord RH, et al. Methamphetamine users entering treatment: characteristics of the methamphetamine treatment project sample. Subst Use Misuse. 2007;42:2207–2222. [PubMed]
- Chumakov I, Blumenfeld M, Guerassimenko O, Cavarec L, Palicio M, Abderrahim H, et al. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci USA. 2002;99:13675–13680. [PMC free article] [PubMed]
- Clemens KJ, Nieuwenhuyzen PS, Li KM, Cornish JL, Hunt GE, McGregor IS. MDMA ("ecstasy"), methamphetamine and their combination: long-term changes in social interaction and neurochemistry in the rat. Psychopharmacology. 2004;173:318–325. [PubMed]
- Clemens KJ, Cornish JL, Hunt GE, McGregor IS. Repeated weekly exposure to MDMA, methamphetamine or their combination: long-term behavioural and neurochemical effects in rats. Drug Alcohol Depend. 2007;86:183–190. [PubMed]
- Clemens KJ, McGregor IS, Hunt GE, Cornish JL. MDMA, methamphetamine and their combination: possible lessons for party drug users from recent preclinical research. Drug Alcohol Rev. 2007;26:9–15. [PubMed]
- Cotter D, Kerwin R, Al-Sarraji S, Brion JP, Chadwich A, Lovestone S, et al. Abnormalities of Wnt signalling in schizophrenia–evidence for neurodevelopmental abnormality. Neuroreport. 1998;9:1379–1383. [PubMed]
- Davis JM, Schlemmer FP., Jr . The amphetamine psychosis. In: Caldwell J, editor. Amphetamines and related stimulants: chemical, biological, clinical and social aspects. Boca Raton: CRC Press; 1980. pp. 161–173.
- Detera-Wadleigh SD, Badner JA, Yoshikawa T, Sanders AR, Goldin LR, Turner G, et al. Initial genome scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 4, 7, 9, 18, 19, 20, and 21q. Am J Med Genet. 1997;74:254–262. [PubMed]
- Edwards TL, Wang X, Chen Q, Wormly B, Riley B, O'Neill FA, et al. Interaction between interleukin 3 and dystrobrevin-binding protein 1 in schizophrenia. Schizophr Res. 2008;106:208–217. [PMC free article] [PubMed]

- Ezaki N, Nakamura K, Sekine Y, Thanseem I, Anitha A, Iwata Y, et al. Short allele of 5-HTTLPR as a risk factor for the development of psychosis in Japanese methamphetamine abusers. Ann N Y Acad Sci. 2008;1139:49–56. [PubMed]
- Fanous AH, Neale MC, Webb BT, Straub RE, O'Neill FA, Walsh D, et al. Novel linkage to chromosome 20p using latent classes of psychotic illness in 270 Irish high-density families. Biol Psychiatry. 2008;64:121–127. [PubMed]
- Fergusson DM, Horwood LF, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med. 2003;33:15–21. [PubMed]
- Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. Annu Rev Pharmacol Toxicol. 2007;47:681–698. [PubMed]
- Fujii D. Risk factors for treatment-resistive methamphetamine psychosis. J Neuropsychiatry Clin Neurosci. 2002;14(2):239–240. [PubMed]
- Futamura T, Akiyama S, Sugino H, Forbes A, McQuade RD, Kikuchi T. Aripiprazole attenuates established behavioral sensitization induced by methamphetamine. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:1115–1119. [PubMed]
- Geyer MA, Markou A. Animal models of psychiatric disorders. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the fourth generation of progress. New York: Raven; 1995. pp. 787–798.
- Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, Rawson R, et al. Clinical course and outcomes of methamphetamine-dependent adults with psychosis. J Subst Abuse Treat. 2008;35:445–450. [PubMed]
- Grant KM, Kelley SS, Agrawal S, Meza JL, Meyer JR, Romberger DJ. Methamphetamine use in rural midwesterners. Am J Addict. 2007;16:79–84. [PubMed]
- Gurling HM, Kalsi G, Brynjolfson J, Sigmundsson T, Sherrington R, Mankoo BS, et al. Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3-24 and 20q12.1-11.23. Am J Hum Genet. 2001;68:661–673. [PMC free article] [PubMed]
- Hadamitzky M, Markou A, Kuczenski R. Extended access to methamphetamine self-administration affects sensorimotor gating in rats. Behav Brain Res. 2011;217:386–390. [PMC free article] [PubMed]
- Harris D, Batki SL. Stimulant psychosis: symptom profile and acute clinical course. Am J Addict. 2000;9:28–37. [PubMed]
- Harrison PJ, Lyon L, Sartorius LJ, Burnet PW, Lane TA. The group II metabotropic glutamate receptor 3 (mGluR3, mGlu3, GRM3): expression, function and involvement in schizophrenia. J Psychopharmacol. 2008;22:308–322. [PubMed]
- Hashimoto T, Hashimoto K, Matsuzawa D, Shimizu E, Sekine Y, Inada T, et al. A functional glutathione S-transferase P1 gene polymorphism is associated with methamphetamine-induced psychosis in Japanese population. Am J Med Genet B Neuropsychiatr Genet. 2005;135B:5–9. [PubMed]
- Huang YY, Battistuzzi C, Oquendo MA, Harkavy-Friedman J, Greenhill L, Zalsman G, et al. Human 5-HT1A receptor C(−1019)G polymorphism and psychopathology. Int J Neuropsychopharmacol. 2004;7:441–451. [PubMed]
- Ide S, Kobayashi H, Tanaka K, Ujike H, Sekine Y, Ozaki N, et al. Gene polymorphisms of the mu opioid receptor in methamphetamine abusers. Ann N Y Acad Sci. 2004;1025:316–324. [PubMed]
- Ide S, Kobayashi H, Ujike H, Ozaki N, Sekine Y, Inada T, et al. Linkage disequilibrium and association with methamphetamine dependence/psychosis of mu-opioid receptor gene polymorphisms. Pharmacogenomics J. 2006;6:179–188. [PubMed]

- Iijima M, Nikaido T, Akiyama M, Moriya T, Shibata S. Methamphetamine-induced, suprachiasmatic nucleus-independent circadian rhythms of activity and mPer gene expression in the striatum of the mouse. Eur J Neurosci. 2002;16:921–929. [PubMed]
- Ikeda M, Iwata N, Suzuki T, Kitajima T, Yamanouchi Y, Kinoshiya Y, et al. Positive association of AKT1 haplotype to Japanese methamphetamine use disorder. Int J Neuropsychopharmacol. 2006;9:77–81. [PubMed]
- Ikeda M, Ozaki N, Suzuki T, Kitajima T, Yamanouchi Y, Kinoshita Y, et al. Possible association of beta-arrestin 2 gene with methamphetamine use disorder, but not schizophrenia. Genes Brain Behav. 2007;6:107–112. [PubMed]
- Inada T, Iijima Y, Uchida N, Maeda T, Iwashita S, Ozaki N, et al. No association found between the type 1 sigma receptor gene polymorphisms and methamphetamine abuse in the Japanese population: a collaborative study by the Japanese Genetics Initiative for Drug Abuse. Ann N Y Acad Sci. 2004;1025:27–33. [PubMed]
- Itoh K, Hashimoto K, Shimizu E, Sekine Y, Ozaki N, Inada T, et al. Association study between brain-derived neurotrophic factor gene polymorphisms and methamphetamine abusers in Japan. Am J Med Genet B Neuropsychiatr Genet. 2005;132B:70–73. [PubMed]
- Iwanami A, Sugiyama A, Kuroki N, Toda S, Kato N, Nakatani Y, et al. Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan. Acta Psychiatr Scand. 1994;89:428–432. [PubMed]
- Iwata N, Inada T, Harano M, Komiyama T, Yamada M, Sekine Y, et al. No association is found between the candidate genes of t-PA/plasminogen system and Japanese methamphetamine-related disorder: a collaborative study by the Japanese Genetics Initiative for Drug Abuse. Ann N Y Acad Sci. 2004;1025:34–38. [PubMed]
- Iyo M, Sekine Y, Mori N. Neuromechanism of developing methamphetamine psychosis: a neuroimaging study. Ann N Y Acad Sci. 2004;1025:288–295. [PubMed]
- Izquierdo A, Belcher AM, Scott L, Cazares VA, Chen J, O'Dell SJ, et al. Reversal-specific learning impairments after a binge regimen of methamphetamine in rats: possible involvement of striatal dopamine. Neuropsychopharmacology. 2010;35:505–514. [PMC free article] [PubMed]
- Jeong SH, Joo EJ, Ahn YM, Lee KY, Kim YS. Investigation of genetic association between human Frizzled homolog 3 gene (FZD3) and schizophrenia: results in a Korean population and evidence from meta-analysis. Psychiatry Res. 2006;143:1–11. [PubMed]
- Joo A, Shibata H, Ninomiya H, Kawasaki H, Tashiro N, Fukumaki Y. Structure and polymorphisms of the human metabotropic glutamate receptor type 2 gene (GRM2): analysis of association with schizophrenia. Mol Psychiatry. 2001;6:186–192. [PubMed]
- Kanahara N, Miyatake R, Sekine Y, Inada T, Ozaki N, Iwata N, et al. Association study between the PIK4CA gene and methamphetamine use disorder in a Japanese population. Am J Med Genet B Neuropsychiatr Genet. 2009;150B:233–238. [PubMed]
- Kantrowitz JT, Malhotra AK, Cornblatt B, Silipo G, Balla A, Suckow RF, et al. High dose D-serine in the treatment of schizophrenia. Schizophr Res. 2010;121:125–130. [PMC free article] [PubMed]
- Kazahaya Y, Akimoto K, Otsuki S. Subchronic methamphetamine treatment enhances methamphetamine- or cocaine-induced dopamine efflux in vivo. Biol Psychiatry. 1989;25:903–912. [PubMed]
- Kew JN, Pflimlin MC, Kemp JA, Mutel V. Differential regulation of synaptic transmission by mGlu2 and mGlu3 at the perforant path inputs to the dentate gyrus and CA1 revealed in mGlu2 −/− mice. Neuropharmacology. 2002;43:215–221. [PubMed]
- Kinoshita Y, Ikeda M, Ujike H, Kitajima T, Yamanouchi Y, Aleksic B, et al. Association study of the calcineurin A gamma subunit gene (PPP3CC) and methamphetamine-use disorder in a Japanese population. Ann N Y Acad Sci. 2008;1139:57–62. [PubMed]

- Kishi T, Ikeda M, Kitajima T, Yamanouchi Y, Kinoshita Y, Kawashima K, et al. Prostate apoptosis response 4 gene is not associated with methamphetamine-use disorder in the Japanese population. Ann N Y Acad Sci. 2008;1139:83–88. [PubMed]
- Kishi T, Ikeda M, Kitajima T, Yamanouchi Y, Kinoshita Y, Kawashima K, et al. A functional polymorphism in estrogen receptor alpha gene is associated with Japanese methamphetamine induced psychosis. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:895–898. [PubMed]
- Kishi T, Tsunoka T, Ikeda M, Kawashima K, Okochi T, Kitajima T, et al. Serotonin 1A receptor gene and major depressive disorder: an association study and meta-analysis. J Hum Genet. 2009;54:629–633. [PubMed]
- Kishi T, Tsunoka T, Ikeda M, Kitajima T, Kawashima K, Okochi T, et al. Serotonin 1A receptor gene is associated with Japanese methamphetamine-induced psychosis patients. Neuropharmacology. 2009;58:452–456. [PubMed]
- Kishi T, Kitajima T, Tsunoka T, Okumura T, Okochi T, Kawashima K, et al. PR0KR2 is associated with methamphetamine dependence in the Japanese population. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:1033–1036. [PubMed]
- Kishimoto M, Ujike H, Motohashi Y, Tanaka Y, Okahisa Y, Kotaka T, et al. The dysbindin gene (DTNBP1) is associated with methamphetamine psychosis. Biol Psychiatry. 2008;63:191–196. [PubMed]
- Kishimoto M, Ujike H, Okahisa Y, Kotaka T, Takaki M, Kodama M, et al. The Frizzled 3 gene is associated with methamphetamine psychosis in the Japanese population. Behav Brain Funct. 2008;4:37. [PMC free article] [PubMed]
- Kobayashi H, Hata H, Ujike H, Harano M, Inada T, Komiyama T, et al. Association analysis of delta-opioid receptor gene polymorphisms in methamphetamine dependence/psychosis. Am J Med Genet B Neuropsychiatr Genet. 2006;141B:482–486. [PubMed]
- Kobayashi H, Ide S, Hasegawa J, Ujike H, Sekine Y, Ozaki N, et al. Study of association between alpha-synuclein gene polymorphism and methamphetamine psychosis/dependence. Ann N Y Acad Sci. 2004;1025:325–334. [PubMed]
- Koizumi H, Hashimoto K, Kumakiri C, Shimizu E, Sekine Y, Ozaki N, et al. Association between the glutathione S-transferase M1 gene deletion and female methamphetamine abusers. Am J Med Genet B Neuropsychiatr Genet. 2004;126B:43–45. [PubMed]
- Konradi C, Heckers S. Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. Pharmacol Ther. 2003;97:153–179. [PMC free article] [PubMed]
- Kosloski LM, Ha DM, Hutter JA, Stone DK, Pichler MR, Reynolds AD, et al. Adaptive immune regulation of glial homeostasis as an immunization strategy for neurodegenerative diseases. J Neurochem. 2010;114:1261–1276. [PMC free article] [PubMed]
- Kotaka T, Ujike H, Morita Y, Kishimoto M, Okahisa Y, Inada T, et al. Association study between casein kinase 1 epsilon gene and methamphetamine dependence. Ann N Y Acad Sci. 2008;1139:43–48. [PubMed]
- Kotaka T, Ujike H, Okahisa Y, Takaki M, Nakata K, Kodama M, et al. G72 gene is associated with susceptibility to methamphetamine psychosis. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:1046–1049. [PubMed]
- Krasnova IN, Cadet JL. Methamphetamine toxicity and messengers of death. Brain Res Rev. 2009;60:379–407. [PMC free article] [PubMed]
- Kuczenski R, Segal DS, Melega WP, Lacan G, McCunney SJ. Human methamphetamine pharmacokinetics simulated in the rat: behavioral and neurochemical effects of a 72-h binge. Neuropsychopharmacology. 2009;34:2430–2441. [PMC free article] [PubMed]
- Kuhn DM, Francescutti-Verbeem DM, Thomas DM. Dopamine disposition in the presynaptic process regulates the severity of methamphetamine-induced neurotoxicity. Ann N Y Acad Sci. 2008;1139:118–126. [PMC free article] [PubMed]

- Lambert D, Gale JA, Hartley D. Substance abuse by youth and young adults in rural America. J Rural Health. 2008;24:221–228. [PubMed]
- Francois B, Czesak M, Steubl D, Albert PR. Transcriptional regulation at a HTR1A polymorphism associated with mental illness. Neuropharmacology. 2008;55:977–985. [PubMed]
- Leamon MH, Flower K, Salo RE, Nordahl TE, Kranzler HR, Galloway GP. Methamphetamine and paranoia: the methamphetamine experience questionnaire. Am J Addict. 2010;19:155–168. [PMC free article] [PubMed]
- Leelahanaj T, Kongsakon R, Netrakom P. A 4-week, double-blind comparison of olanzapine with haloperidol in the treatment of amphetamine psychosis. J Med Assoc Thai. 2005;88(suppl 3):S43–S52. [PubMed]
- Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, et al. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci. 2003;23:8788–8799. [PubMed]
- Lemonde S, Du L, Bakish D, Hrdina P, Albert PR. Association of the C(−1019)G 5-HT1A functional promoter polymorphism with antidepressant response. Int J Neuropsychopharmacol. 2004;7:501–506. [PubMed]
- Li T, Chen CK, Hu X, Ball D, Lin SK, Chen W, et al. Association analysis of the DRD4 and COMT genes in methamphetamine abuse. Am J Med Genet B Neuropsychiatr Genet. 2004;129B:120–124. [PubMed]
- Li W, Zhang Q, Oiso N, Novak EK, Gautam R, O'brien EP, et al. Hermansky-Pudlak syndrome type 7 (HPS-7) results from mutant dysbindin, a member of the biogenesis of lysosome-related organelles complex 1 (BLOC-1) Nat Genet. 2003;35:84–89. [PMC free article] [PubMed]
- Liu HC, Lin SK, Liu SK, Chen SL, Hu CJ, Chang JG, et al. DAT polymorphism and diverse clinical manifestations in methamphetamine abusers. Psychiatr Genet. 2004;14:33–37. [PubMed]
- Liu HC, Chen CK, Leu SJ, Wu HT, Lin SK. Association between dopamine receptor D1 A-48 G polymorphism and methamphetamine abuse. Psychiatry Clin Neurosci. 2006;60:226–231. [PubMed]
- Lucas FR, Salinas PC. WNT-7a induces axonal remodeling and increases synapsin I levels in cerebellar neurons. Dev Biol. 1997;192:31–44. [PubMed]
- Lyon L, Kew JN, Corti C, Harrison PJ, Burnet PW. Altered hippocampal expression of glutamate receptors and transporters in GRM2 and GRM3 knockout mice. Synapse. 2008;62:842–850. [PMC free article] [PubMed]
- Machiyama Y. Chronic methamphetamine intoxication model of schizophrenia in animals. Schizophr Bull. 1992;18:107–113. [PubMed]
- Maehara S, Hikichi H, Satow A, Okuda S, Ohta H. Antipsychotic property of a muscarinic receptor agonist in animal models of schizophrenia. Pharmacol Biochem Behav. 2008;91:140–149. [PubMed]
- Mahoney JJ, 3rd, Kalechstein AD, Garza R, 2nd, Newton TF. Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependence participants. Am J Addict. 2008;17:83–98. [PMC free article] [PubMed]
- Manschreck TC, Laughery JA, Weisstein CC, Allen D, Humblestone B, Neville M, et al. Characteristics of freebase cocaine psychosis. Yale J Biol Med. 1988;61:115–122. [PMC free article] [PubMed]
- Markou A, Chiamulera C, Geyer MA, Tricklebank M, Steckler T. Removing obstacles in neuroscience drug discovery: the future path for animal models. Neuropsychopharmacology. 2009;34:74–89. [PMC free article] [PubMed]
- Martinez V, Parikh V, Sarter M. Sensitized attentional performance and Fos-immunoreactive cholinergic neurons in the basal forebrain of amphetamine-pretreated rats. Biol Psychiatry. 2005;57:1138–1146. [PubMed]

- Matsumoto T, Karmijo A, Miyakawa T, Endo K, Yabana T, Kishimoto H, et al. Methamphetamine in Japan: the consequences of methamphetamine abuse as a function of route of administration. Addiction. 2002;97:809–817. [PubMed]
- Matsuzawa D, Hashimoto K, Miyatake R, Shirayama Y, Shimizu E, Maeda K, et al. Identification of functional polymorphisms in the promoter region of the human PICK1 gene and their association with methamphetamine psychosis. Am J Psychiatry. 2007;164:1105–1114. [PubMed]
- Mccreary AC, Jones CA. Antipsychotic medication: the potential role of 5-HT(1A) receptor agonism. Curr Pharm Des. 2010;16:516–521. [PubMed]
- McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. Addiction. 2006;101:1473–1478. [PubMed]
- McKetin R, Ross J, Kelly E, Baker A, Lee N, Lubman DI, et al. Characteristics and harms associated with injecting versus smoking methamphetamine among methamphetamine treatment entrants. Drug Alcohol Rev. 2008;27:277–285. [PubMed]
- Misra LK, Kofoed L, Oesterheld JR, Richards GA. Olanzapine treatment of methamphetamine psychosis. J Clin Psychopharmacol. 2000;20:393–394. [PubMed]
- Mizoguchi H, Arai S, Koike H, Ibi D, Kamei H, Nabeshima T, et al. Therapeutic potential of nicotine for methamphetamine-induced impairment of sensorimotor gating: involvement of pallidotegmental neurons. Psychopharmacology. 2009;207:235–243. [PubMed]
- Moos RH, Brennan PL, Mertens JR. Diagnostic subgroups and predictors of one-year re-admission among late-middle-aged and older substance abuse patients. J Stud Alcohol. 1994;55:173–183. [PubMed]
- Morio A, Ujike H, Nomura A, Tanaka Y, Morita Y, Otani K, et al. No association between CART (cocaine- and amphetamine-regulated transcript) gene and methamphetamine dependence. Ann N Y Acad Sci. 2006;1074:411–417. [PubMed]
- Morita Y, Ujike H, Tanaka Y, Uchida N, Nomura A, Ohtani K, et al. A nonsynonymous polymorphism in the human fatty acid amide hydrolase gene did not associate with either methamphetamine dependence or schizophrenia. Neurosci Lett. 2005;376:182–187. [PubMed]
- Morita Y, Ujike H, Tanaka Y, Uchida N, Nomura A, Otani K, et al. The X-box binding protein 1 (XBP1) gene is not associated with methamphetamine dependence. Neurosci Lett. 2005;383:194–198. [PubMed]
- Morita Y, Ujike H, Tanaka Y, Kishimoto M, Okahisa Y, Kotaka T, et al. The glycine transporter 1 gene (GLYT1) is associated with methamphetamine-use disorder. Am J Med Genet B Neuropsychiatr Genet. 2008;147B:54–58. [PubMed]
- Mosley RL, Gendelman HE. Control of neuroinflammation as a therapeutic strategy for amyotrophic lateral sclerosis and other neurodegenerative disorders. Exp Neurol. 2010;222:1–5. [PMC free article] [PubMed]
- Nakama H, Chang L, Cloak C, Jiang C, Alicata D, Haning W. Association between psychiatric symptoms and craving in methamphetamine users. Am J Addict. 2008;17:441–446. [PMC free article] [PubMed]
- Nakamura K, Chen CK, Sekine Y, Iwata Y, Anitha A, Loh El W, et al. An association study of monoamine oxidase A (MAOA) gene polymorphism in methamphetamine psychosis. Neurosci Lett. 2009;455:120–123. [PubMed]
- Nestler EJ. Molecular neurobiology of addiction. Am J Addict. 2001;10:201–217. [PubMed]
- Ng KL, Li JD, Cheng MY, Leslie FM, Lee AG, Zhou QY. Dependence of olfactory bulb neurogenesis on prokineticin 2 signaling. Science. 2005;308:1923–1927. [PubMed]
- Nishikawa T, Mataga N, Takashima M, Toru M. Behavioral sensitization and relative hyperresponsiveness of striatal and limbic dopaminergic neurons after repeated methamphetamine treatment. Eur J Pharmacol. 1983;88:195–203. [PubMed]

- Nishiyama T, Ikeda M, Iwata N, Suzuki T, Kitajima T, Yamanouchi Y, et al. Haplotype association between GABAA receptor gamma2 subunit gene (GABRG2) and methamphetamine use disorder. Pharmacogenomics J. 2005;5:89–95. [PubMed]
- NSDUH Substance Abuse and Mental Health Services Administration (2009) Results from the 2008 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09–4434) Rockville, MD, pp 242–243
- Ohgake S, Hashimoto K, Shimizu E, Koizumi H, Okamura N, Koike K, et al. Functional polymorphism of the NQO2 gene is associated with methamphetamine psychosis. Addict Biol. 2005;10:145–148. [PubMed]
- Okahisa Y, Ujike H, Kotaka T, Morita Y, Kodama M, Inada T, et al. Association between neuropeptide Y gene and its receptor Y1 gene and methamphetamine dependence. Psychiatry Clin Neurosci. 2009;63:417–422. [PubMed]
- Okochi T, Kishi T, Ikeda M, Kitajima T, Kinoshita Y, Kawashima K, et al. Genetic association analysis of NRG1 with methamphetamine-induced psychosis in a Japanese population. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:903–905. [PubMed]
- Okuyama S, Chaki S, Kawashima N, Suzuki Y, Ogawa S, Kumagai T, et al. The atypical antipsychotic profile of NRA0045, a novel dopamine D4 and 5-hydroxytryptamine2A receptor antagonist, in rats. Br J Pharmacol. 1997;121:515–525. [PMC free article] [PubMed]
- Pulver AE, Lasseter VK, Kasch L, Wolyniec P, Nestadt G, Blouin JL, et al. Schizophrenia: a genome scan targets chromosomes 3p and 8p as potential sites of susceptibility genes. Am J Med Genet. 1995;60:252–260. [PubMed]
- Rawson RA, Gonzales R, Brethen P. Treatment of methamphetamine use disorder: an update. J Subst Abuse Treat. 2002;23:145–150. [PubMed]
- Reichel CM, Schwendt M, McGinty J, Olive MF, See RE (2011) Loss of object recognition memory produced by extended access to methamphetamine self-administration is reversed by positive allosteric modulation of metabotropic glutamate receptor 5. Neuropsychopharmacology [advance online publication] [PMC free article] [PubMed]
- Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res. 1986;396:157–198. [PubMed]
- Ross J, Berrettini W, Coryell W, Gershon ES, Badner JA, Kelsoe JR, et al. Genome-wide parametric linkage analyses of 644 bipolar pedigrees suggest susceptibility loci at chromosomes 16 and 20. Psychiatr Genet. 2008;18:191–198. [PMC free article] [PubMed]
- Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. Eur J Pharmacol. 2003;479:23–40. [PubMed]
- Rounsaville BJ, Anton SF, Carroll K, Budde D, Prusoff BA, Gawin F. Psychiatric diagnoses of treatment-seeking cocaine abusers. Arch Gen Psychiatry. 1991;48:43–51. [PubMed]
- Salo R, Nordahl TE, Leamon MH, Natsuaki Y, Moore CD, Waters C, et al. Preliminary evidence of behavioral predictors of recurrent drug-induced psychosis in methamphetamine abuse. Psychiatry Res. 2008;157:273–277. [PubMed]
- SAMHSA [Substance Abuse and Mental Health Services Administration], Office of Applied Studies (2009) Treatment Episode Data Set (TEDS) 1998–2008, National Admissions to Substance Abuse Treatment Services, Drugs and Alcohol Services Information System Series: S-50, HHS Publication No. (SMA) 09–4471, Rockville, MD, 52
- Sartorius LJ, Weinberger DR, Hyde TM, Harrison PJ, Kleinman JE, Lipska BK. Expression of a GRM3 splice variant is increased in the dorsolateral prefrontal cortex of individuals carrying a schizophrenia risk SNP. Neuropsychopharmacology. 2008;33:2626–2634. [PubMed]
- Sato M. A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. Ann N Y Acad Sci. 1992;654:160–170. [PubMed]

- Schumacher J, Jamra RA, Freudenberg J, Becker T, Ohlraun S, Otte AC, et al. Examination of G72 and D-amino-acid oxidase as genetic risk factors for schizophrenia and bipolar affective disorder. Mol Psychiatry. 2004;9:203–207. [PubMed]
- Segal DS, Mandell AJ. Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. Pharmacol Biochem Behav. 1974;2:249–255. [PubMed]
- Segal DS, Geyer MA, Schuckit MA. Stimulant-induced psychosis: an evaluation of animal methods. Essays Neurochem Neuropharmacol. 1981;5:95–129. [PubMed]
- Segal DS, Kuczenski R. Repeated binge exposures to amphetamine and methamphetamine: behavioral and neurochemical characterization. J Pharmacol Exp Ther. 1997;282:561–573. [PubMed]
- Segal DS, Kuczenski R. Escalating dose-binge treatment with methylphenidate: role of serotonin in the emergent behavioral profile. J Pharmacol Exp Ther. 1999;291:19–30. [PubMed]
- Sekine Y, Iyo M, Ouchi Y, Matsunaga T, Tsukada H, Okada H, et al. Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. Am J Psychiatry. 2001;158:1206–1214. [PubMed]
- Sekine Y, Minabe Y, Ouchi Y, Takei N, Iyo M, Nakamura K, et al. Association of dopamine transporter loss in the orbitofrontal and dorsolateral prefrontal cortices with methamphetamine-related psychiatric symptoms. Am J Psychiatry. 2003;160:1699–1701. [PubMed]
- Shinba T, Yamamoto K, Cao GM, Mugishima G, Andow Y, Hoshino T. Effects of acute methamphetamine administration on spacing in paired rats: investigation with an automated video-analysis method. Prog Neuropsychopharmacol Biol Psychiatry. 1996;20:1037–1049. [PubMed]
- Shoptaw S, Peck J, Reback FJ, Rotheram-Fuller E. Psychiatric and susbstance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependenct gay and bisexual men seeking outpatient drug abuse treatment. J Psychoactive Drugs. 2003;35(Suppl1):161–168. [PubMed]
- Srisurapanont M, Ali R, Marsden J, Sunga A, Wada K, Monteiro M. Psychotic symptoms in methamphetamine psychotic in-patients. Int J Neuropsychopharmacol. 2003;6:347–352. [PubMed]
- Stone DK, Reynolds AD, Mosley RL, Gendelman HE. Innate and adaptive immunity for the pathobiology of Parkinson's disease. Antioxid Redox Signal. 2009;11:2151–2166. [PMC free article] [PubMed]
- Straub RE, Jiang Y, Maclean CJ, Ma Y, Webb BT, Myakishev MV, et al. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet. 2002;71:337–348. [PMC free article] [PubMed]
- Suzuki A, Nakamura K, Sekine Y, Minabe Y, Takei N, Suzuki K, et al. An association study between catechol-O-methyl transferase gene polymorphism and methamphetamine psychotic disorder. Psychiatr Genet. 2006;16:133–138. [PubMed]
- Takigawa M, Maeda H, Ueyama K, Tominaga H, Matsumoto K. A dual approach to self-stimulation and locomotor trace affected by chronic methamphetamine treatment for an animal model of schizophrenia. Can J Physiol Pharmacol. 1993;71:321–325. [PubMed]
- Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ, et al. Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. J Clin Invest. 2004;113:1353–1363. [PMC free article] [PubMed]
- Thomas DM, Francescutti-Verbeem DM, Liu X, Kuhn DM. Identification of differentially regulated transcripts in mouse striatum following methamphetamine treatment–an oligonucleotide microarray approach. J Neurochem. 2004;88:380–393. [PubMed]
- Thomas DM, Walker PD, Benjamins JA, Geddes TJ, Kuhn DM. Methamphetamine neurotoxicity in dopamine nerve endings of the striatum is associated with microglial activation. J Pharmacol Exp Ther. 2004;311:1–7. [PubMed]

- Thomas DM, Francescutti-Verbeem DM, Kuhn DM. The newly synthesized pool of dopamine determines the severity of methamphetamine-induced neurotoxicity. J Neurochem. 2008;105:605–616. [PMC free article] [PubMed]
- Thomas DM, Francescutti-Verbeem DM, Kuhn DM. Methamphetamine-induced neurotoxicity and microglial activation are not mediated by fractalkine receptor signaling. J Neurochem. 2008;106:696–705. [PMC free article] [PubMed]
- Tsunoka T, Kishi T, Kitajima T, Okochi T, Okumura T, Yamanouchi Y, et al. Association analysis of GRM2 and HTR2A with methamphetamine-induced psychosis and schizophrenia in the Japanese population. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:639–644. [PubMed]
- Ujike H. Stimulant-induced psychosis and schizophrenia: the role of sensitization. Curr Psychiatry Rep. 2002;4:177–184. [PubMed]
- Ujike H, Sato M. Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. Ann NY Acad Sci. 2004;1025:279–287. [PubMed]
- Ujike H, Ogawa N, Otsuki S. Effects of acute and long-term treatment with methamphetamine on substance P concentration and receptor numbers in the rat brain. Brain Res. 1988;453:136–142. [PubMed]
- Ujike H, Onoue T, Akiyama K, Hamamura T, Otsuki S. Effect of selective D-1 and D-2 dopamine antagonists on development of methamphetamine-induced behavioral sensitization. Psychopharmacology. 1989;98:89–92. [PubMed]
- Ujike H, Kanzaki A, Okumura K, Akiyama K, Otsuki S. Sigma (sigma) antagonist BMY 14802 prevents methamphetamine-induced sensitization. Life Sci. 1992;50:PL129–PL134. [PubMed]
- Ujike H, Harano M, Inada T, Yamada M, Komiyama T, Sekine Y, et al. Nine- or fewer repeat alleles in VNTR polymorphism of the dopamine transporter gene is a strong risk factor for prolonged methamphetamine psychosis. Pharmacogenomics J. 2003;3:242–247. [PubMed]
- Ujike H, Sakai A, Nakata K, Tanaka Y, Kodaka T, Okahisa Y, et al. Association study of the dihydropyrimidinase-related protein 2 gene and methamphetamine psychosis. Ann N Y Acad Sci. 2006;1074:90–96. [PubMed]
- Ujike H, Katsu T, Okahisa Y, Takaki M, Kodama M, Inada T, et al. Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset and poor prognosis of methamphetamine psychosis. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:625–629. [PubMed]
- UNODC United Nations Office on Drugs and Crime, World Drug Report (2009) http://www.unodc.org/documents/scientific/ATS/Global-ATS-Assessment-2009-Web.pdf, 280
- Utena H. A special type of model psychosis: a chronic methamphetamine intoxication in man and animal. Brain Nerve. 1961;13:687–692.
- Utena H. Behavioral aberrations in methamphetamine-intoxicated animals and chemical correlates in the brain. Prog Brain Res. 1966;21B:192–207. [PubMed]
- Os J, Bak M, Hanssen M, Bijl RV, Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population based study. Am J Epidemiol. 2002;156:319–327. [PubMed]
- Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry. 2001;158:2015–2021. [PubMed]
- Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, et al. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci. 2001;21:9414–9418. [PubMed]
- Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry. 2001;158:377–382. [PubMed]

- Volz TJ, Fleckenstein AE, Hanson GR. Methamphetamine-induced alterations in monoamine transport: implications for neurotoxicity, neuroprotection and treatment. Addiction. 2007;102(Suppl 1):44–48. [PubMed]
- Wallace C, Galloway T, McKetin R, Kelly E, Leary J. Methamphetamine use, dependence and treatment access in rural and regional North Coast of New South Wales, Australia. Drug Alcohol Rev. 2009;28:592–599. [PubMed]
- Wang HY, Liu T, Malbon CC. Structure-function analysis of Frizzleds. Cell Signal. 2006;18:934–941. [PubMed]
- Wang Y, Zhang J, Mori S, Nathans J. Axonal growth and guidance defects in Frizzled3 knock-out mice: a comparison of diffusion tensor magnetic resonance imaging, neurofilament staining, and genetically directed cell labeling. J Neurosci. 2006;26:355–364. [PubMed]
- Weickert CS, Miranda-Angulo AL, Wong J, Perlman WR, Ward SE, Radhakrishna V, et al. Variants in the estrogen receptor alpha gene and its mRNA contribute to risk for schizophrenia. Hum Mol Genet. 2008;17:2293–2309. [PMC free article] [PubMed]
- Weisner C, Mertens J, Parthasarathy S, Moore C, Hunkeler EM, Hu T, et al. The outcome and cost of alcohol and drug treatment in an HMO: day hospital versus traditional outpatient regimens. Health Serv Res. 2000;35:791–812. [PMC free article] [PubMed]
- Wilson JM, Kalasinsky KS, Levey AI, Bergeron C, Reiber G, Anthony RM, et al. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat Med. 1996;2:699–703. [PubMed]
- Xu W, Zhu JP, Angulo JA. Induction of striatal pre- and postsynaptic damage by methamphetamine requires the dopamine receptors. Synapse. 2005;58:110–121. [PMC free article] [PubMed]
- Yagi M. Factors influencing the general activity in rats: 2. Effects of methamphetamine. Ann Anim Psychol. 1963;13:37–47.
- Yang J, Si T, Ling Y, Ruan Y, Han Y, Wang X, et al. Association study of the human FZD3 locus with schizophrenia. Biol Psychiatry. 2003;54:1298–1301. [PubMed]
- Yen CF, Chong MY. Comorbid psychiatric disorders, sex, and methamphetamine use in adolescents: a case-control study. Compr Psychiatry. 2006;47:215–220. [PubMed]
- Yoo JH, Cho JH, Yu HS, Lee KW, Lee BH, Jeong SM, et al. Involvement of 5-HT receptors in the development and expression of methamphetamine-induced behavioral sensitization: 5-HT receptor channel and binding study. J Neurochem. 2006;99:976–988. [PubMed]
- Yoshikawa T, Lin SK, Mori N. Association analysis of SOD2 variants with methamphetamine psychosis in Japanese and Taiwanese populations. Hum Genet. 2006;120:243–252. [PubMed]
- Yue W, Kang G, Zhang Y, Qu M, Tang F, Han Y, et al. Association of DAOA polymorphisms with schizophrenia and clinical symptoms or therapeutic effects. Neurosci Lett. 2007;416:96–100. [PubMed]
- Yui K, Goto K, Ikemoto S, Ishiguro T, Kamada Y. Increased sensitivity to stress and episode recurrence in spontaneous recurrence of methamphetamine psychosis. Psychopharmacology. 1999;145:267–272. [PubMed]
- Yui K, Ikemoto S, Ishiguro T, Goto K. Studies of amphetamine or methamphetamine psychosis in Japan: relation of methamphetamine psychosis to schizophrenia. Ann N Y Acad Sci. 2000;914:1–12. [PubMed]
- Zhang Y, Yu X, Yuan Y, Ling Y, Ruan Y, Si T, et al. Positive association of the human frizzled 3 (FZD3) gene haplotype with schizophrenia in Chinese Han population. Am J Med Genet B Neuropsychiatr Genet. 2004;129B:16–19. [PubMed]
- Zweben JE, Cohen JB, Christian D, Galloway GP, Salinardi M, Parent D, et al. Psychiatric symptoms in methamphetamine users. Am J Addict. 2004;13:181–190. [PubMed]

CERTIFICATE OF SERVICE

I certify under penalty of perjury under the laws of the State of Washington that on November 26, 2018, I caused to be served electronically a copy of the foregoing in the Division II Court of Appeals, which will also effectively serve the State, and also caused a hard copy to be sent via U.S. mail to Petitioner James Charles Mathes, DOC #931439, at: Washington State Penitentiary, 1313 North 13th Avenue, Walla Walla, WA 99362.

DATED at Seattle, Washington, this 26th day of November, 2018.

LAW OFFICES OF JOHN HENRY BROWNE, P.S.

/s/ Kimberly Hennessey
Kimberly Hennessey

LAW OFFICES OF JOHN HENRY BROWNE, P.S.

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