Cerebrospinal fluid levels of monoamines among suicide attempters: A systematic review and random-effects meta-analysis

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Running title: CSF monoamines among suicide attempters

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Abstract

Background: It remains unclear whether the dopaminergic and noradrenergic systems may be implied in suicide attempt risk. In addition, although the serotonergic system has been extensively studied, no formal meta-analysis has been performed to examine its association with suicide attempt.

Methods: Using PRISMA methodology, we performed a systematic literature review and random-effects *meta-analyses* of the differences in cerebrospinal fluid (CSF) levels of 5-HIAA, HVA and MHPG between suicide attempters and individuals who never attempted suicide.

Results: We identified 30 studies including 937 suicide attempters and 1128 non-attempters; 29 of them measured CSF levels of 5-HIAA, 22 measured CSF levels of HVA and 14 measured CSF levels of MHPG. CSF levels of 5-HIAA and HVA were significantly lower in suicide attempters than in non-attempters [SMD= -0.43 (95% CI: -0.71 to -0.15; $p<0.01$) and SMD= -0.45 (95% CI: -0.72 to -0.19; $p<0.01$), respectively]. We did not find a significant association between CSF MHPG levels and suicide attempt.

Limitations: Our analyses relied on a limited number of studies of good quality and most studies included small sample sizes.

Conclusion: Both serotonin and dopamine systems may play a role in suicide attempt risk. Our findings suggest that a silo approach to biomarkers should be phased out in favor of the study of multiple systems in parallel and in the same populations to progress in the

identification of the biological components independently associated with suicide risk, with the goal of identifying new treatment targets and improving suicide risk prediction.

Key words: suicide attempt; serotonin; dopamine; noradrenalin; biomarker; cerebrospinal fluid; violent; meta-analysis.

Disclaimer

The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the US government.

Introduction

Worldwide, about 800,000 people take their own life every year ("WHO | Preventing suicide," 2017). To date, suicide risk assessment is based solely on clinical evaluations, which are hampered by the elevated number of medical, psychological and social predictors, their frequent co-occurrence, and their limited predictive power (Geoffroy et al., 2020; Ghasemi, Shaghaghi, & Allahverdipour, 2015; Kovacs, Beck, & Weissman, 1975; Hamilton, 1960; Hoertel et al., 2015, 2018; Maris, 2002; McMahon et al., 2018; Oquendo, Currier, & Mann, 2006; Oquendo, Perez-Rodriguez, et al., 2014; Pascal de Raykeer et al., 2018; Peyre et al., 2017; Posner et al., 2011; Sheer et al., 2020). The lack of robust clinical predictors of suicide risk has led researchers to search for biomarkers that may help improve suicide risk prediction and suggest mechanism-based specific interventions.

The stress–diathesis model posits that suicidal behavior is triggered by a stressful life event or a psychiatric episode in an individual with a predisposing diathesis (van Heeringen and Mann, 2014). Several lines of evidence implicate dysregulation in stress response

systems, especially the hypothalamic-pituitary-adrenal (HPA) axis, and abnormalities in the serotonergic system, as a diathesis for suicide risk (Oquendo, Sullivan, et al., 2014). However, the HPA axis is linked to other biological systems, such as the serotonergic, opioid, and glutamate systems, inflammatory pathways, lipid status, and neuroplasticity or neurogenesis system (Oquendo, Sullivan, et al., 2014), suggesting that a battery of biomarkers, rather than a single one, will likely be needed to identify the components underlying this diathesis.

The earliest promising cerebrospinal fluid (CSF) monoamine biomarkers of suicidality were the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the dopamine metabolite homovanillic acid (HVA), and the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (Asberg et al., 1976; Engström, Alling, Blennow, Regnéll, & Träskman-Bendz, 1999; Gardner, Lucas, & Cowdry, 1990; Linnoila et al., 1983). A literature review published in 1995 (Lester, 1995) indicated that most studies found significantly decreased levels of CSF levels of 5-HIAA among suicide attempters compared to non-attempters, whereas most studies did not find significantly decreased CSF levels of HVA or MHPG among suicide attempters compared to non-attempters. However, that review examined each study individually and did not use meta-analytic methods to obtain pooled estimates of the associations between suicide attempt and CSF levels of these monoamines. Furthermore, multiple studies have been conducted since 1995, allowing for increased power to examine those associations. Another literature review (Mann et al., 2006) indicated that CSF levels of 5-HIAA may be useful to predict suicide in mood disorders, although with limited positive predictive value. However, no study to date has established quantitatively synthesized results on this association. Thus, there is a need to re-examine whether CSF levels of 5-HIAA, HVA and MHPG are significantly associated with suicide attempt and to estimate the magnitude of those associations.

Such knowledge is essential to advancing our understanding of the neurobiological mechanisms underlying suicidal behaviors. Specifically, the dopaminergic system and noradrenergic system have received relatively limited attention in the past decade as potential contributors to the predisposing diathesis for suicide risk (Oquendo, Sullivan, et al., 2014). However, dopamine, acting through multiple receptors, may play a substantial role in suicidal behavior as it exerts a stimulatory role on the activation of the HPA axis in response to a severe stressor and is involved in the maintenance of post-stress activation of the HPA axis (Belda and Armario, 2009). Some findings also suggest lower norepinephrine function in suicide risk (Oquendo, Sullivan, et al., 2014), which, if confirmed, could indicate either a direct contribution to suicidal behavior or reflect norepinephrine depletion due to down-regulation in excessive response to stress (Oquendo, Sullivan, et al., 2014). Finally, although the serotonergic system has been extensively studied in suicide, we did not find any report of formal meta-analysis of the associations between suicide attempt and CSF levels of 5-HIAA. Therefore, examining if CSF levels of serotonin, dopamine and norepinephrine metabolites are significantly decreased in suicide attempters constitutes an important step to help identify relevant potential biomarkers of suicide risk and guide future research aiming at clarifying the role of each and their interplay, with the ultimate goal of identifying new treatment targets and improving suicide risk prediction (Fischer and Ullsperger, 2017; Niederkofler et al., 2015; Seo et al., 2008).

In this report, we performed a systematic literature review and the first random-effects meta-analysis of the associations of CSF levels of serotonin, dopamine and norepinephrine metabolites (i.e., 5-HIAA, HVA and MHPG) with suicide attempt. Because prior research (Asberg & Träskman, 1981; Lester, 1995) has suggested that abnormalities in neurotransmitters levels in individuals who attempted suicide might be more characteristic of those who use violent methods (i.e., suicide attempt by hanging, drowning, gunshot wound,

gas poisoning, or multiple deep cuts) rather than less violent ones (i.e., oral drug overdoses or single wrist cuts), we also examined CSF levels of these metabolites among suicide attempters who used violent methods.

1.0. Material and methods

1.1. Protocol and registration

This study is a systematic literature review of trials and meta-analyses performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer et al., 2015). The study protocol has been registered in the international prospective register of systematic reviews (PROSPERO, CRD42019125208).

1.2. Outcomes

The primary outcome was the difference in CSF levels of 5-HIAA, HVA and MHPG between suicide attempters and controls (i.e., individuals who had no history of attempted suicide). The secondary outcome was the difference in CSF levels of these metabolites between individuals who made a violent suicide attempt versus those who had no history of attempted suicide.

1.3. Search criteria

We searched for all studies that examined CSF levels of 5-HIAA, HVA and MHPG in suicide attempters. The search was conducted on March 2019 using PUBMED, WEB OF SCIENCE, EMBASE and SCOPUS. Potential gray literature was identified searching in OPENGREY database. We used the following key words: [Suicide attempt] AND [CSF] AND ([5-HIAA] OR [HVA] OR [MHPG]). To ensure a complete search, we also used the following key words: [Suicidal] AND [CSF] AND ([5-HIAA] OR [HVA] OR [MHPG]) NOT

[Suicide attempt]. Studies cited in the reference list of each eligible systematic review were also examined and included in this review if they fulfilled eligibility criteria.

1.4. Eligibility criteria

We restricted our search to case control and cohort studies published between January 1980 and December 2019, including both women and men without any age limitation. Studies that did not include a control group or did not measure, among attempters, CSF levels of monoamines after the suicide attempt were excluded. Although studies in which lumbar puncture was performed within two weeks of the administration of any psychotropic medication or that did not specify the date of last use of psychotropic medications were included in the main analyses, sensitivity analyses excluding them were also performed to examine the robustness of the findings. If full text articles were not available or if there were missing values of CSF levels of metabolites, authors were systematically contacted by electronic mail.

1.5. Data collection process

Two authors (JFC and HC) conducted the search. They first examined all titles and abstracts independently. Then, they independently extracted the data using a standard form as described below. Disagreements in study eligibility or data extraction were resolved by consensus. The flowchart is given in **eFigure 1**. Of the 106 articles meeting eligibility criteria, 74 records were excluded because the studies did not include any measure of CSF levels of monoamines after the suicide attempt (n=61) or a control group (n=13), and 30 articles matched eligibility criteria and were included in qualitative and quantitative synthesis.

1.6. Data collected

Using a standardized form, we systematically recorded from each eligible article the following data: publication date, authors' names, study quality according to the Newcastle-Ottawa Scale (Williams, Gierisch, McDuffie, Strauss, & Nagi, 2011), sample size, participants' age and sex and their main psychiatric diagnosis, medication taken before the lumbar puncture, suicide attempt type based on the suicide method used [categorized as violent (i.e., suicide attempt by hanging, drowning, gunshot wound, gas poisoning, or multiple deep cuts), non-violent (i.e., oral drug overdoses or single wrist cuts) and non-specified], scores on suicide scales, and CSF levels of 5-HIAA, HVA and MHPG.

To rate studies' quality (good, fair and poor), values were attributed to each grade of the Newcastle-Ottawa Scale by awarding stars in each domain following the guidelines of the Newcastle–Ottawa Scale. We used the following cut-offs: association of 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes was referred to as "good" quality score; association of 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes was referred as to "fair" quality score; finally, 0 or 1 star in selection, or 0 star in comparability, or 0 or 1 star in outcomes reflected a "poor" quality score. We used those cut-offs as done in prior research (Sharmin et al., 2017a, 2017b; Vivekanantham et al., 2019).

1.7. Statistical analysis

We used random-effects meta-analysis models, which assume that the observed estimates of CSF levels of 5-HIAA, HVA and MHPG can vary across studies because of real differences in each study as well as sampling variability (Riley et al., 2011). Measures of associations are presented as standardized mean difference (SMD), also known as Cohen's *d* (Cohen, 2013). Heterogeneity was assessed using the I^2 statistic and Tau^2. The I^2 score represents the percentage of variation across studies due to heterogeneity, and ranges from 0 to 100 %; higher values indicate greater heterogeneity across studies (Higgins et al., 2003).

Tau^2 estimates represent the between-study variance in a random-effects meta-analysis. A Tau^2 value greater than 1 suggests the presence of substantial heterogeneity, whereas a value close to 0 indicates homogeneity, meaning that all studies show the same effect (Borenstein, Hedges, & Rothstein, 2007; Deeks, Higgins, & Altman, 2008; Suijkerbuijk et al., 2017). Publication bias was assessed using a funnel plot.

If I^2 was above 25%, a meta-regression analysis was performed to explain statistical heterogeneity in terms of study-level variables. Random-effects meta-regression analyses quantified the association of certain sociodemographic characteristics [age, sex (i.e. male-to-female ratio in cases / male-to-female ratio in controls), the region of the World where the study has been performed, which has been dichotomized into Europe and North America as only 1 study was conducted elsewhere], and diagnosis (i.e., mood disorders *versus* schizophrenia, mood disorders *versus* other psychiatric diagnoses (i.e. other than mood or schizophrenia), and schizophrenia *versus* other psychiatric diagnoses) of studies' participants with study-level effects. Studies were weighted by the inverse of the sum of the within- and between-study variance. Analyses were performed on complete cases.

We also performed *post-hoc* power analyses to determine whether potential non-significant associations might have resulted from limited statistical power (Valentine et al., 2010). To examine the robustness of our results, we repeated those analyses while including only studies of good quality according to the Newcastle-Ottawa Scale. Because psychotropic medications are known to influence CSF concentrations of monoamine metabolites (Scheepers, Wied, Westenberg, & Kahn, 2001; Sheline, Bardgett, & Csernansky, 1997), additional sensitivity analyses were done while excluding studies in which lumbar puncture was performed within two weeks of the administration of any psychotropic medication and those that did not specify the date of last use of psychotropic medications. These analyses were performed using the function "metareg" of R package "meta" (Schwartze, 2012).

Statistical analyses were performed using the R package "meta" (Schwartze, 2012) and statistical significance was evaluated using a two-sided design with α set at 0.05.

2.0. Results

2.1. Characteristics of studies included in the meta-analysis

Thirty case control studies were included in the present analysis (**Table 1**), involving 2065 participants, of which 937 attempted suicide and 1128 did not attempt suicide. Most studies (i.e. 53.3%, N=16) were performed in Europe, 43.3% (N=13) in North America, and 3.3% (N=1) in India.

Of these 30 studies, 10 studies (33.3%) included participants with mood disorders (9 studies comprised individuals with unipolar depression and 1 study included individuals with bipolar depression), 2 studies (6.7%) focused on individuals with schizophrenia, 4 studies (13.3%) comprised participants with other psychiatric diagnoses (e.g. personality disorders), and 14 (46.7%) included mixed populations (i.e. individuals with different diagnoses).

In addition, of these studies, 29 (96.7%) examined CSF 5-HIAA levels, including 906 suicide attempters and 1051 controls (mean age=40.2 years (SD=8.3), sex ratio=0.7); 22 (73.3%) examined CSF levels of HVA, including 666 suicide attempters and 861 controls (mean age=41.1 years (SD=8.8), sex ratio=0.8); and 14 (46.7%) explored CSF levels of MHPG, including 465 suicide attempters and 529 controls (mean age=38.1 years (SD=6.4), sex ratio=0.7). Finally, 10 (33.3%) studies focused on violent suicide attempts.

2.2. *5-HIAA*

2.2.1. *Full sample*

Of 29 studies, 12 found that suicide attempt was significantly associated with lower CSF 5-HIAA levels, 2 indicated a significant association in the opposite direction, and 15

reported a non-significant association. (**Figure 1a**). This heterogeneity could not be explained by age (95% CI: -0.053 to 0.035; p=0.6864, N=21) or sex (95% CI: -1.157 to 0.829; p=0.7460, N=14) or diagnosis (other psychiatric diagnoses (n=4) versus mood disorders (n=9): 95% CI: -3.330 to 1.274; p-value=0.6527; other psychiatric diagnoses (n=4) versus schizophrenia (n=2): 95% CI: 0.174 to 1.736; p-value=0.1091; mood disorders (n=9) versus schizophrenia (n=2): 95% CI: -0.061 to 2.460; p-value=0.0622). However, it could be partially explained by the region of the World where the study has been conducted (Europe versus North America: 95% CI: -1.186 to -0.063; p=0.0292, N=28) (**eFigure 2**). In the analyses restricted to the studies conducted in Europe, we found a significant association as obtained in the full sample [SMD= -0.69 (95% CI: -1.13 to -0.24), p=0.0026, Tau^2=0.70, I^2=0.89], but not in studies restricted to North America [SMD= -0.05 (95% CI: -0.32 to 0.23), p=0.7363, Tau^2=0.13, I^2=0.64]. Sensitivity analysis restricted to the 18 studies of good or fair quality (n=1411, mean age=38.2 years (SD=6.0), sex ratio=1.1) yielded similar significant results [SMD= -0.31 (95% CI: -0.61 to -0.02), p=0.0038, Tau^2=0.32, I^2=0.84] (**Figure 1b**).

2.2.2. *Violent suicide attempts*

Ten studies (n=595) compared CSF 5-HIAA levels between 126 violent suicide attempters and 469 controls (mean age=38.4 years (SD=6.4), sex ratio=0.8) (**eFigure 3a**). Of these 10 studies, 5 found that violent suicide attempt was significantly associated with lower CSF 5-HIAA levels and 5 reported a non-significant association. Results from the random-effects meta-analysis showed that CSF 5-HIAA levels were significantly lower in violent suicide attempters than in controls [SMD= -0.90 (95% CI: -1.47; -0.32), p=0.0024, Tau^2=0.70, I^2=0.84]. This heterogeneity was not explained by age (95% CI: −0.011 to 0.134; p=0.0953; N=7) or sex (95% CI: −1.535 to 0.902; p=0.6108; N=6) or the region of the World where the study has been conducted (95% CI: −1.932 to 0.555; p=0.2776; N=10) or diagnosis

(other psychiatric diagnoses (n=1) versus mood disorders (n=2): 95% CI: -2.058 to 0.212, p-value=0.1108; mood disorders (n=2) versus schizophrenia (n=1): 95% CI: -2.039 to 0.249, p-value=0.1251). Sensitivity analysis restricted to the 7 studies of good or fair quality (n=328, mean age=37.4 years (SD=6.4), sex ratio=0.8) yielded similar results [SMD= -1.05 (95% CI: -1.78 to -0.31), p=0.0051, Tau^2=0.82, I^2=0.87] (**eFigure 3b**). A sensitivity analysis restricted to the 19 studies comparing CSF 5-HIAA levels between 527 non-violent suicide attempters and 582 controls (mean age=41.1 years (SD=9.2), sex ratio=0.7) showed that CSF 5-HIAA levels were significantly lower in non-violent suicide attempters than in controls [SMD= -0.49 (95% CI: -0.91; -0.06), p=0.0253, Tau^2=0.73, I^2=0.89] (**eFigure 4**). Finally, additional meta-regression analysis indicated that CSF levels of 5-HIAA did not significantly differ between individuals who did a violent versus a non-violent suicide attempt (SMD=-0.4115; 95% CI= -1.1351 to 0.3122, p-value=0.2651).

2.3. HVA

2.3.1. *Full sample*

Five studies found that suicide attempt was significantly associated with lower CSF HVA levels and 17 studies reported a non-significant association. Random-effects meta-analysis of these studies showed that CSF HVA levels were significantly lower in suicide attempters than in non-attempters [SMD= -0.45 (95% CI: -0.72 to -0.19), p=0.0008, Tau^2=0.30, I^2=0.80] (**Figure 2a**). This heterogeneity could be partially explained by the age of participants (95% CI: −0.105 to -0.019; p=0.0051, N=16) (**eFigure 5**), but not by sex (95% CI, −0.203 to 1.410, p=0.1423, N=12) or the region of the World where the study has been conducted (95% CI: −0.244 to 0.848, p=0.2788, N=22) or diagnosis (other psychiatric diagnoses (n=3) versus mood disorders (n=6): 95% CI: -1.824 to 0.361, p-value=0.1893; other psychiatric diagnoses (n=3) versus schizophrenia (n=1): 95% CI: -0.187 to 0.442, p-

value=0.4281; mood disorders (n=6) versus schizophrenia (n=1): 95% CI: -0.944 to 2.882, p-value=0.3208). Sensitivity analysis restricted to the 16 studies of good or fair quality (n=1104, mean age=36.2 years (SD=6.8)) yielded similar results [SMD= -0.43 (95% CI: -0.69 to -0.17), p=0.0014, Tau^2=0.21, I^2=0.75] (**Figure 2b**).

2.3.2. *Violent suicide attempts*

Seven studies (n=416) compared CSF HVA levels between 108 violent suicide attempters and 308 controls (mean age=36.6 (SD=6.9), sex ratio=0.7) (**eFigure 6a**). Of these studies, none reported a significant association between CSF HVA levels and violent suicide attempts. Results from the random-effects meta-analysis showed a negative trend towards significance between CSF HVA levels and violent suicide attempt [SMD = -0.16 (95% CI: -0.39 to 0.07), p=0.1746, Tau^2=0.00, I^2=0.00]. Sensitivity analysis restricted to the 6 studies of good or fair quality (n=309, mean age=36.6 years (SD=6.9), sex ratio=0.7) yielded similar results [SMD= -0.23 (95% CI: -0.48 to 0.03), p=0.0866, Tau^2=0.00, I^2=0.00] (**eFigure 6b**). Sensitivity analysis restricted to the 15 studies comparing CSF HVA levels between 336 non-violent suicide attempters and 553 controls (mean age=43.1 years (SD=9.1), sex ratio=0.71) showed that CSF HVA levels were significantly lower in non-violent suicide attempters than in controls [SMD= -0.67 (95% CI: -1.06; -0.27), p=0.0009, Tau^2=0.47, I^2=0.83] (**eFigure 7**). Finally, additional meta-regression analysis indicated that CSF levels of HVA did not significantly differ between individuals who did a violent versus a non-violent suicide attempt (SMD=0.5156; 95%CI: -0.0855; 1.1166, p-value=0.0927).

2.4. MHPG

2.4.1. *Full sample*

Twelve studies reported a non-significant association, 2 found that suicide attempt was significantly associated with lower CSF MHPG levels and 1 found an association in the opposite direction. Results from the random-effects meta-analysis of these studies did not show an association between CSF MHPG levels and suicide attempt [SMD= -0.33 (95% CI: -0.77 to 0.11), p=0.1407, Tau^2=0.61, I^2=0.89] (**Figure 3a**). This high heterogeneity could not be explained by age (95% CI, −0.123 to 0.052; p = 0.4207, N = 11) or sex (95% CI, −1.990 to 0.692; p = 0.3426, N=8) or the region of the World where the study has been conducted (95% CI, −0.654 to 1.197; p=0.5657, N=14). However, it could be at least partially explained by the diagnosis of participants included in the studies (other psychiatric diagnoses (n=3) versus mood disorders (n=3): 95% CI: -0.853 to 0.848, p-value=0.9957; other psychiatric diagnoses (n=3) versus schizophrenia (n=1): 95% CI: 0.314 to 1.725, p-value=0.0046; mood disorders (n=3) versus schizophrenia (n=1): 95% CI: 1.231 to 2.753, p-value<0.0001). In the single study conducted among participants with schizophrenia, there was an association between suicide attempt and higher CSF MHPG levels [SMD=1.71 (95% CI: 1.08 to 2.34), p<0.0001], whereas we did not find a significant association between CSF MHPG levels and suicide attempt among participants with mood disorders [SMD= -0.28 (95% CI: -0.68 to 0.12), p=0.1698] or other psychiatric diagnoses [SMD= -0.33 (95% CI: -1.04 to 0.39), p=0.3725]. Sensitivity analysis restricted to the 11 studies of good or fair quality (n=753, mean age=37.5 years (SD=6.4), sex ratio=0.8) yielded similar results [SMD= -0.31 (95% CI: -0.86; 0.24), p= 0.2621, Tau^2=0.77, I^2=0.91] (**Figure 3b**).

2.4.2. *Violent suicide attempts*

Three studies (n=160, sex ratio=1.1, mean age=39.5 years (SD=0.6)) compared CSF MHPG levels between 41 violent suicide attempters and 119 controls (**eFigure 8**). None of these studies reported a significant association between CSF MHPG levels and violent suicide

attempts. Results from the random-effects meta-analysis of these studies showed a non-significant association between CSF MHPG levels and violent suicide attempts [SMD= -0.20 (95% CI: -0.79 to 0.38), p-value=0.4955, Tau^2=0.15, I^2=0.58] (**eFigure 8**). Additional meta-regression analysis indicated that CSF levels of MHPG did not significantly differ between individuals who did a violent versus a non-violent suicide attempt (SMD= 0.3337; 95%CI: -0.6840; 1.3513, p-value=0.5205).

2.5. Publication bias

Funnel plots of studies comparing CSF levels of 5-HIAA, HVA and MHPG between suicide attempters and controls highlighted relatively symmetrical plots, with few studies with elevated standard errors for 5-HIAA and HVA studies, and none for MHPG studies, suggesting a low likelihood of publication estimates bias (**Figure 4**). In addition, sensitivity analyses excluding study outliers did not modify the significance of our results.

2.6. Post-hoc power analyses

Statistical power for detecting a small effect size of SMD=0.2 was >80% for random-effects meta-analysis models of 5-HIAA studies (i.e., 86.1%) and HVA studies (i.e., 83.0%). However, it was lower for MHPG studies (i.e., 60.2%), for which our meta-analysis had 80% power to detect a SMD of 0.3. For meta-analysis models performed in individuals who made violent suicide attempts, statistical power for detecting a small effect size of SMD=0.2 was limited, at 27.4% for 5-HIAA studies, 23.2% for HVA studies and 13.6% for MHPG studies.

4. Discussion

In the first meta-analysis to our knowledge of the relationship between CSF levels of serotonin, dopamine and norepinephrine metabolites and suicide attempt, we found that

suicide attempt was significantly associated with diminished CSF levels of 5-HIAA and HVA. These results suggest that lower serotonin and dopamine levels in the central nervous system may be implicated in suicide attempts. The magnitude of these associations was small to medium, with effect sizes of 0.43 for CSF 5-HIAA and 0.45 for CSF HVA.

While the finding of lower CSF levels of 5-HIAA among suicide attempters converges with prior research (Asberg & Träskman, 1981; Lester, 1995), we also found a significant association between diminished CSF levels of HVA and suicide attempt, contrasting with a previous literature review (Lester, 1995). The use of meta-analytic methods, which combine estimates from multiple studies to increase statistical power, permitted detection of an effect that had been previously concealed by the examination of individual studies. Associations of diminished CSF levels of 5-HIAA and HVA with violent and non-violent suicide attempt were all significant, except for that between CSF HVA levels and violent suicide attempt, which showed only a trend towards significance, possibly because of limited statistical power. These results suggest that differences in CSF levels of 5-HIAA and HVA may not be specific to violent suicide attempts but rather associated with suicide attempt regardless of the method used. Finally, in accord with a prior literature review (Lester, 1995), but contrasting with some findings suggesting lower norepinephrine function in suicide risk (Oquendo, Sullivan, et al., 2014), we did not find a significant association between CSF MHPG levels and suicide attempt. Because our meta-analysis had 80% power to detect a SMD of at least 0.3 for CSF MHPG levels, our study suggests that any association between CSF MHPG levels and suicide attempt, if it exists, is likely to be small.

The finding of a possible implication of serotonin in suicide attempts is consistent with prior research. Prior genetic studies, although not all (Brezo et al., 2008; Lutz et al., 2017), have found that serotonin transporter genetic polymorphisms (Clayden et al., 2012; Daray et al., 2018; de Medeiros Alves et al., 2015; Lee et al., 2015; Li and He, 2007), tryptophan

hydroxylase (TPH) genetic polymorphism (Bellivier et al., 2004; Clayden et al., 2012; Pawlak et al., 2016) and serotonin receptor genetic polymorphisms (Pawlak et al., 2016) may influence suicide risk. Moreover, prior studies suggest that individuals with a lifetime history of suicide attempt who have low CSF 5-HIAA levels may be at greater risk for reattempting or completing suicide (Nordström et al., 1994; Roy et al., 1989; Träskman et al., 1981). Prior research also supports the potential implication of impaired serotoninergic system in violent behaviors (Fanelli and Serretti, 2019; Gerra et al., 2004; Hallikainen et al., 1999) and the lower plasma 5-HIAA and platelet 5-HT concentrations in suicide attempters compared to healthy controls (Spreux-Varoquaux et al., 2001). Finally, our results are also in line with studies indicating that use of SSRIs may be associated with a reduced risk of suicide in adults with major depressive disorder (Barbui et al., 2009).

Importantly, we found that the dopaminergic system may play a substantial role in suicide attempt, in line with several findings. A prior study suggested that patients with major depression who had attempted suicide may have a greater reduction in urinary metabolites of dopamine than depressed non-attempter individuals or healthy controls (Roy et al., 1992). Fitzgerald et al., 2017 also found in a post-mortem analysis of brain tissue of 17 individuals who died by suicide a loss of correlation between D1 and D2 receptor binding, suggesting a dysregulation of dopamine receptors. Bowden et al. (Bowden et al., 1997) previously showed a reduction of dihydroxyphenylacetic acid, a dopamine metabolite, in the caudate, putamen and nucleus accumbens in a postmortem study of depressed individuals who died by suicide. Finally, our results are also consistent with studies indicating that use of ketamine, which may increase dopamine levels in the cortex, the striatum and the nucleus accumbens (Kokkinou et al., 2018) through a downstream effect from its glutamatergic effects, may lead to short-term reductions in suicidal ideation (Murrough et al., 2015; Wilkinson et al., 2018).

Our study has important implications. First, our results suggest that both the serotoninergic pathway and the dopaminergic pathway may be implicated in suicide attempts. Specifically, dopamine has received relatively little attention as a potential contributor to suicide risk, especially recently (Oquendo, Sullivan, et al., 2014). However, dopamine may play a substantial role in suicidal behavior due to its stimulatory role on the activation of the HPA axis in response to a severe stressor and involvement in the maintenance of post-stress activation of the HPA axis (Belda and Armario, 2009), which evinces multilevel dysfunction associated with increased suicide risk (Oquendo, Sullivan, et al., 2014). Furthermore, serotonin and dopamine interact with each other (Daw et al., 2002; Di Giovanni et al., 2010, 2008; Esposito, 2006; Olvera-Cortés et al., 2008) and may be both involved in the individual's ability to cope with suicidal thoughts (Ryding et al., 2008). Serotonin-dopamine interaction may act as a moderator of decision making (Rogers, 2011), commonly observed to be impaired during suicidal crises (Szanto et al., 2015). Interactions between serotonin and dopamine systems in the prefrontal cortex may also underlie the link between impulsive aggression and suicidal behavior (Seo et al., 2008). Whether serotonergic and dopaminergic abnormalities observed in individuals who attempted suicide or have died by suicide are independent of each other or stress response abnormalities remains a crucial unanswered question. Taken together, these findings suggest that a silo approach to biomarkers should be phased out in favor of the study of multiple systems in parallel and in the same populations to progress in the identification of the components independently associated with suicide risk, with the goal of identifying new treatment targets and improving suicide risk prediction. Finally, our results suggest that differences in CSF levels of metabolites of serotonin and dopamine may not be specific to violent suicide attempts, but rather associated with suicide attempt regardless of the method used, suggesting that these biomarkers might be useful in predicting all types of suicide attempt. However, since there are likely different biological

pathways to suicide attempt, future work on the neurobiology of suicide risk would benefit in using finer-grained phenotyping of suicidal behavior, based for example on patterns of suicidal thinking and stress responsivity (Bernanke et al., 2017), to examine whether each potential biomarker candidate is specific to one or different suicidal behavior phenotypes.

Our study has several limitations. First, most studies included in our meta-analysis relied on small sample sizes (i.e., less than 30 participants). However, our meta-analysis models examining the relationship between suicide attempt and CSF levels of 5-HIAA, HVA and MHPG were appropriately powered (i.e. ≥80%) to detect a small effect size of SMD=0.3. Second, an important issue is whether the biochemical abnormalities observed in our study are independent of psychiatric diagnosis. Because only a minority of studies included participants with the same psychiatric diagnosis, our study was insufficiently powered to perform analyses stratified by diagnosis (e.g. only one study measured CSF HVA levels among suicide attempters with schizophrenia). Although we did not find any significant moderating effect of the diagnosis of participants on the association between suicide attempt and CSF levels of 5-HIAA and HVA, future studies are needed to examine this issue. Third, our analyses relied on a limited number of studies of good quality. However, our significant results held in sensitivity analyses restricted to good or fair quality. Fourth, in all studies except one (Chatzittofis et al., 2013), individuals were prescribed psychotropic medications, which are known to influence CSF concentrations of monoamine metabolites (Scheepers et al., 2001; Sheline et al., 1997), and date of last use of psychotropic medications varied substantially across studies. However, the exclusion of studies in which lumbar puncture was performed within two weeks of the administration of any psychotropic medication and those that did not specify when participants used for the last time psychotropic medications, did not alter the significance of our results. Fifth, measures of association do not necessarily imply causal association (Le Strat and Hoertel, 2011). Finally, we cannot rule out that some

significant results, such as the moderating effects of participants' characteristics, might result from type I error inflation due to multiple testing.

Research implications

Whether serotonergic and dopaminergic abnormalities in individuals who attempted suicide are independent of each other or stress response abnormalities is a crucial unanswered question. Our findings suggest that a silo approach to biomarkers should be phased out in favor of the study of multiple systems in parallel and in the same populations to progress in the identification of the components independently associated with suicide risk, with the goal of identifying new treatment targets and improving suicide risk prediction.

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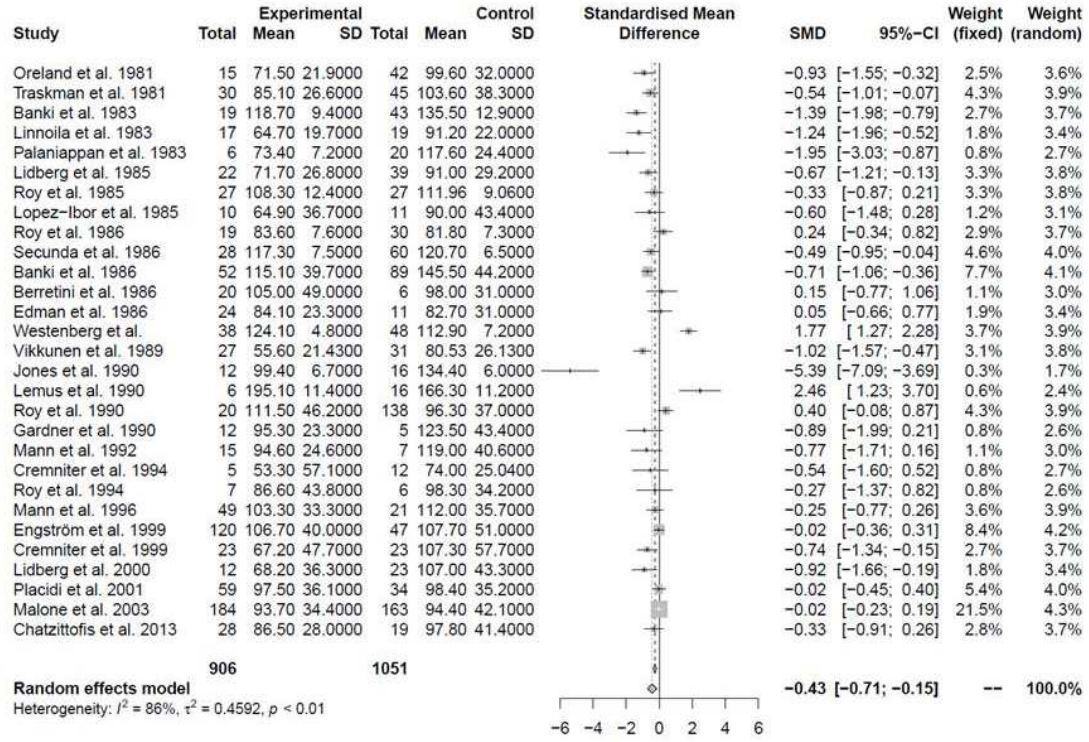
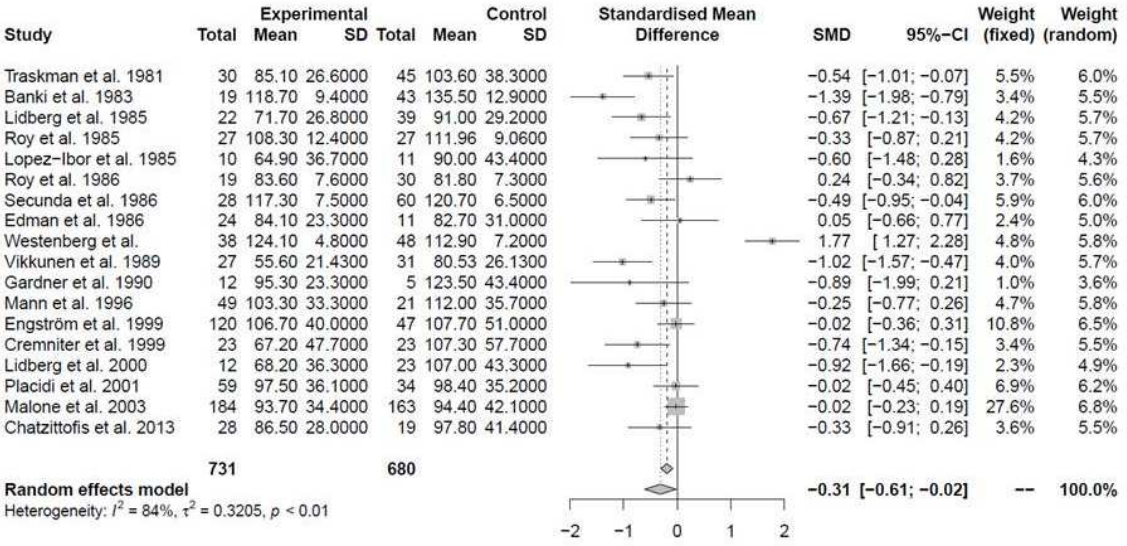
Figure 1. Forest plot comparing CSF 5-HIAA levels between suicide attempters and non-attempters using a random-effects meta-analysis model.

A



A. CSF 5-HIAA levels were significantly lower in suicide attempters than in controls [SMD= -0.43 (95% CI: -0.71; -0.15), p=0.0026]

B

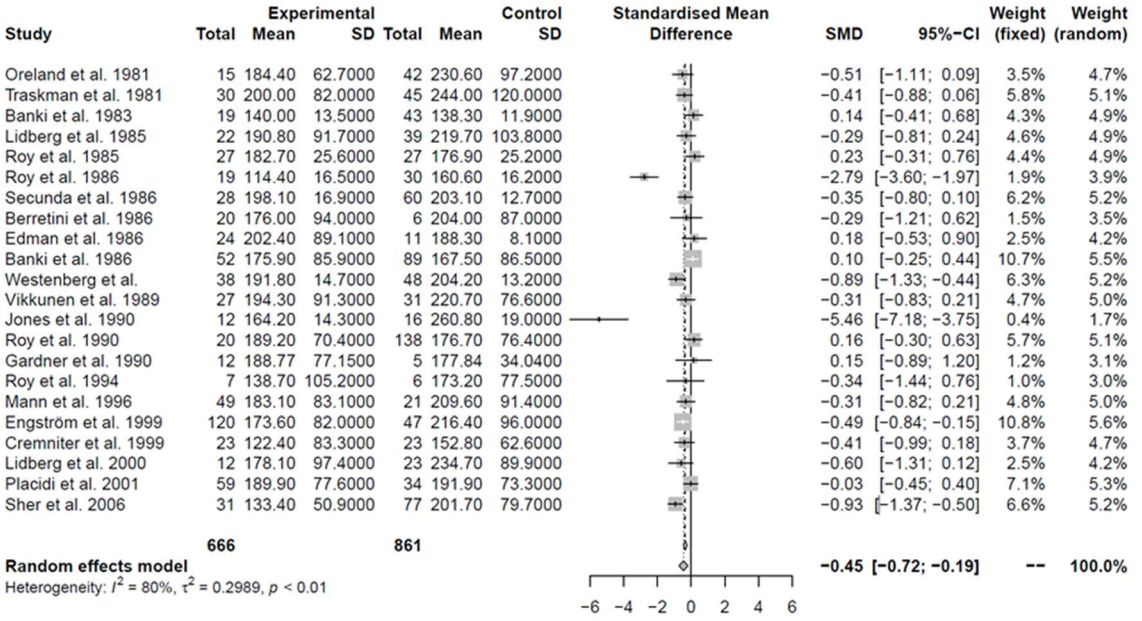


B. Sensitivity analysis restricted to the 18 studies of good or fair quality [SMD= -0.31 (95% CI: -0.61 to -0.02), p=0.0038]

A. Meta-analysis of all studies. **B.** Meta-analysis restricted to studies of good and fair quality according to the Newcastle-Ottawa Scale.
Size of squares is proportional to study weights. Diamond marker indicates pooled effect size.

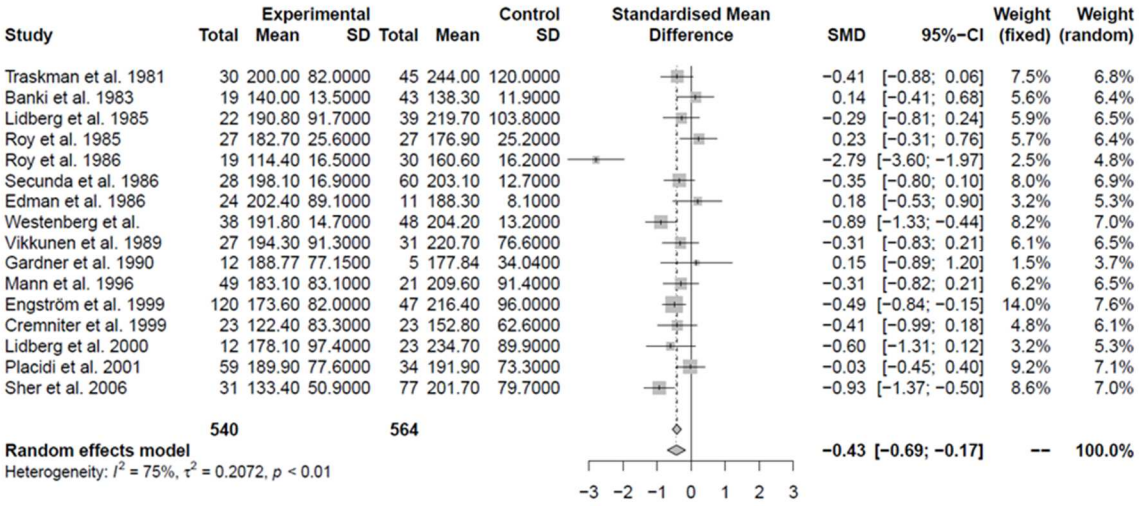
Figure 2. Forest plot comparing CSF HVA levels between suicide attempters and non-attempters using a random-effects meta-analysis model.

A.



A. CSF HVA levels were significantly lower in suicide attempters than in controls [SMD= -0.45 (95% CI: -0.72 to -0.19), p=0.0008]

B.

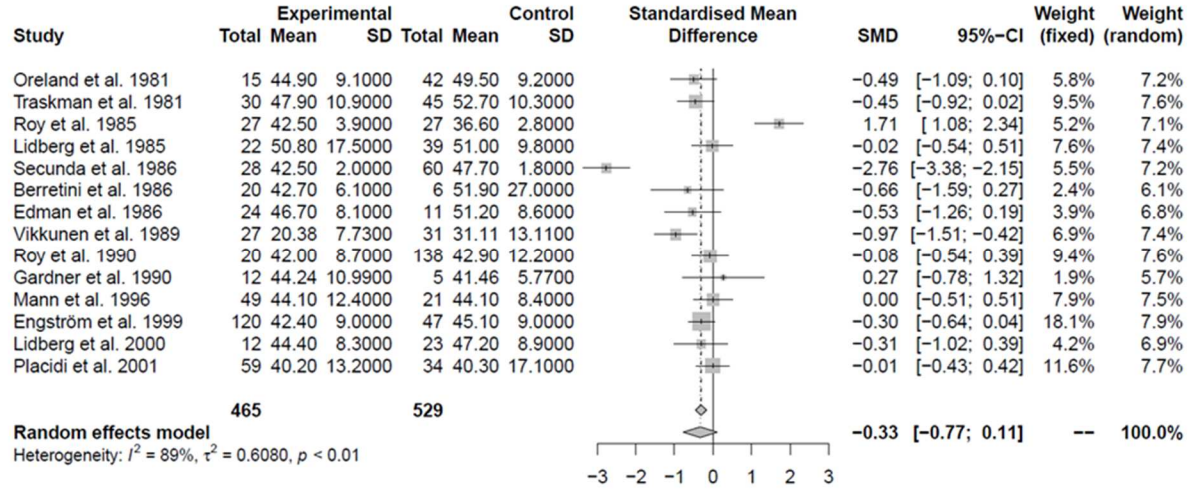


B. Sensitivity analysis restricted to the 16 studies of good or fair quality [SMD= -0.43 (95% CI: -0.69 to -0.17), p=0.0014]

A. Meta-analysis of all studies. **B.** Meta-analysis restricted to studies of good and fair quality according to the Newcastle-Ottawa Scale.
Size of squares is proportional to study weights. Diamond marker indicates pooled effect size.

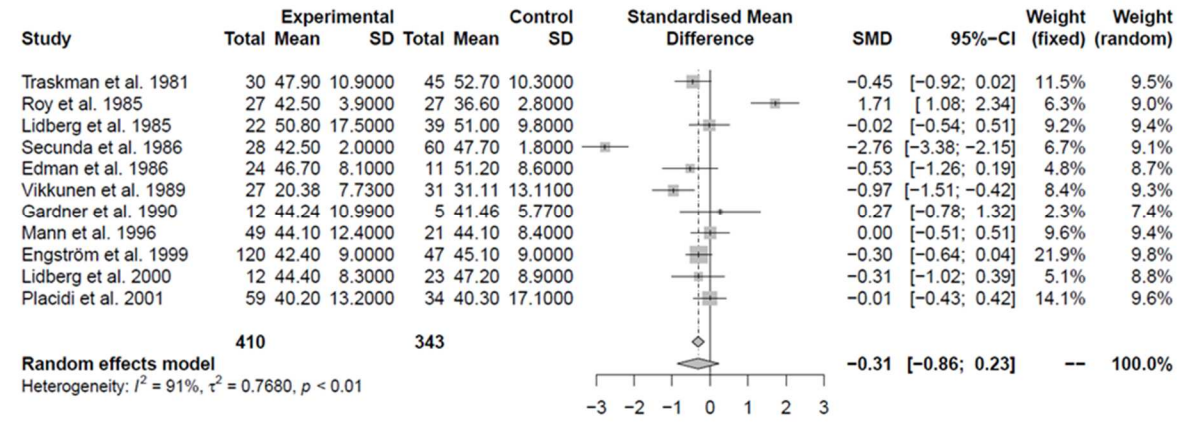
Figure 3. Forest plot comparing CSF MHPG levels between suicide attempters and non-attempters using a random-effects meta-analysis model.

A.



A. CSF MHPG levels did not show an association with suicide attempt [SMD= -0.33 (95% CI: -0.77 to 0.11), p=0.1407

B.

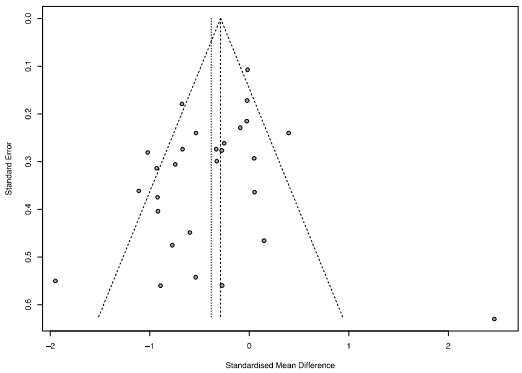


B. Sensitivity analysis restricted to the 11 studies of good or fair quality yielded similar results [SMD= -0.31 (95% CI: -0.86; 0.24), p= 0.2621

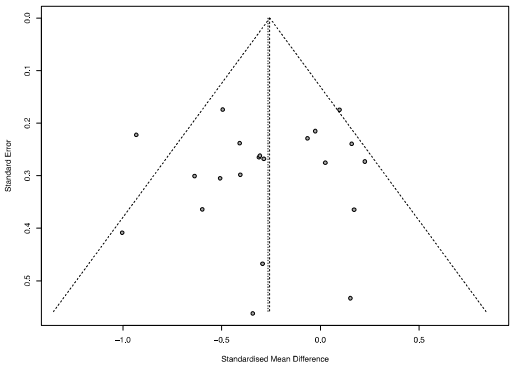
A. Meta-analysis of all studies. **B.** Meta-analysis restricted to studies of good and fair quality according to the Newcastle-Ottawa Scale.
Size of squares is proportional to study weights. Diamond marker indicates pooled effect size.

Figure 4. Funnel plots of studies comparing CSF levels of 5-HIAA, HVA and MHPG between suicide attempters and non-attempters.

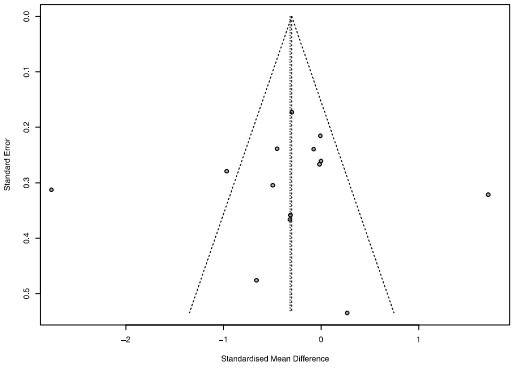
A



B



C



A. Studies examining CSF 5-HIAA levels; **B.** Studies examining CSF HVA levels; C. Studies examining CSF MHPG levels.
Each dot represents a study; the *y*-axis represents study precision and the *x*-axis shows the study's average effect size.

Table 1. Clinical information on studies included in the analysis (N=30).

ARTICLES (year of publication)	Sample Size			AGE [m (SD)]		Diagnosis	Region of the World	CSF Metabolites
	Controls (i.e. non-attempters) (W/M)	Suicide Attempters (W/M)	Violent SA	Controls	Suicide Attempters			
(Chatzittofis et al., 2013)	19 (7/12)	28 (10/18)		30.0 (-)	41 (12.3)	mixed	Europe	5-HIAA
(Sher et al., 2006)	77 (39/38)	31 (16/15)		40.0 (17.3)	41.3 (15.4)	unipolar depression	North America	HVA
(Malone et al., 2003)	163 (-/-)	184 (-/-)		-	-	mixed	North America	5-HIAA
(Placidi et al., 2001)	34 (21/13)	59 (33/26)		38.0 (12.9)	34.4 (10)	mixed	North America	5-HIAA, HVA, MHPG
(Lidberg et al., 2000)	23 (0/23)	12 (0/12)		35.7 (-)	30.3 (-)	mixed	Europe	5-HIAA, HVA, MHPG
(Cremniter et al., 1999)	23 (5/18)	23 (5/18)	23	47.1 (15.5)	37.7 (13.1)	mixed	Europe	5-HIAA, HVA
(Engström et al., 1999)	47 (17/30)	120 (65/55)	26	44.1 (15.9)	38.2 (13.2)	mixed	Europe	5-HIAA, HVA, MHPG
(Mann et al., 1996)	21 (10/11)	49 (25/21)	17	49.3 (14.7)	40.7 (16.4)	mixed	North America	5-HIAA, HVA, MHPG
(Mann et al., 1992)	7 (-/-)	15 (-/-)		-	-	unipolar depression	North America	5-HIAA
(Roy and Pollack, 1994)	6 (-/-)	7 (-/-)		-	-	unipolar depression	North America	5-HIAA, HVA
(Cremniter et al., 1994)	12 (-/-)	5 (-/-)	5	-	32.6 (8.8)	unipolar depression	Europe	5-HIAA
(Gardner et al., 1990)	5 (5/0)	12 (12/0)		-	-	other	North America	5-HIAA, HVA, MHPG
(Roy et al., 1990)	138 (-/-)	20 (-/-)	5	44.9 (14.0)	42.3 (12.3)	other	North America	5-HIAA, HVA, MHPG
(Lemus et al., 1990)	16 (3/13)	6 (3/3)		-	-	schizophrenia	North America	5-HIAA
(Jones et al., 1990)	16 (-/-)	12 (-/-)		67.6 (7.0)	63.2 (6.8)	mixed	Europe	5-HIAA, HVA
(Virkkunen et al., 1989)	31 (0/31)	27 (0/27)		28.6 (10.3)	32.0 (9.6)	other	Europe	5-HIAA, HVA, MHPG
(Westenberg and Verhoeven, 1988)	48 (27/21)	38 (21/17)		53.5 (2.0)	52.2 (2.0)	mixed	Europe	5-HIAA, HVA

(Edman et al., 1986)	11 (5/6)	24 (17/7)	8	40.0 (12.3)	41.7 (12.7)	unipolar depression	Europe	5-HIAA, HVA, MHPG
(Berrettini et al., 1986)	6 (-/-)	20 (-/-)		-	-	bipolar depression	North America	5-HIAA, HVA, MHPG
(Banki et al., 1986)	89 (-/-)	52 (-/-)	18	-	-	mixed	Europe	5-HIAA, HVA
(Secunda et al., 1986)	60 (38/32)	28 (13/15)		50.9 (1.8)	39.0 (2.3)	mixed	North America	5-HIAA, HVA, MHPG
(Roy et al., 1986)	30 (16/14)	19 (16/3)		32.2 (2.5)	41.1 (2.6)	unipolar depression	North America	5-HIAA, HVA
(López-Ibor et al., 1985)	11 (7/4)	10 (8/2)		46.8 (15.24)	46.3 (15.54)	unipolar depression	Europe	5-HIAA
(Roy et al., 1985)	27 (13/14)	27 (12/15)	7	25.2 (8.3)	25.5 (4.3)	schizophrenia	North America	5-HIAA, HVA, MHPG
(Lidberg et al., 1985)	39 (0/39)	22 (0/22)		39.1 (11.3)	41.4 (13.4)	unipolar depression	Europe	5-HIAA, HVA, MHPG
(Palaniappan et al., 1983)	20 (-/-)	6 (-/-)		36.55 (8.5)	35.3 (7.9)	unipolar depression	India	5-HIAA
(Linnoila et al., 1983)	19 (0/19)	17 (0/17)		-	-	other	Europe	5-HIAA
(Banki and Arató, 1983)	43 (43/0)	19 (19/0)	6	-	-	mixed	Europe	5-HIAA, HVA
(Träskman et al., 1981)	45 (17/28)	30 (19/11)	8	40.0 (10)	37.0 (10)	mixed	Europe	5-HIAA, HVA, MHPG
(Oreland et al., 1981)	42 (14/28)	15 (10/5)		-	-	mixed	Europe	5-HIAA, HVA, MHPG

CSF=Cerebrospinal fluid; HVA=homovanillic acid; m=mean; M=Men; sd=standard deviation; W=Women; MHPG=3-methoxy-4-hydroxyphenylglycol; 5-HIAA=5-hydroxy indoleacetic acid.
- refers to missing values in the article.