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# Ethanol-induced alterations of amino acids measured by *in vivo* microdialysis in rats: a meta-analysis

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## Abstract

**Purpose:** In recent years *in vivo* microdialysis has become an important method in research studies investigating the alterations of neurotransmitters in the extracellular fluid of the brain. Based on the major involvement of glutamate and  $\gamma$ -aminobutyric acid (GABA) in mediating a variety of alcohol effects in the mammalian brain, numerous microdialysis studies have focused on the dynamical behavior of these systems in response to alcohol.

**Methods:** Here we performed multiple meta-analyses on published datasets from the rat brain: (i) we studied basal extracellular concentrations of glutamate and GABA in brain regions that belong to a neurocircuitry involved in neuropsychiatric diseases, especially in alcoholism (Noori et al., *Addict Biol* 17:827-864, 2012); (ii) we examined the effect of acute ethanol administration on glutamate and GABA levels within this network and (iii) we studied alcohol withdrawal-induced alterations in glutamate and GABA levels within this neurocircuitry.

**Results:** For extraction of basal concentrations of these neurotransmitters, datasets of 6932 rats were analyzed and the absolute basal glutamate and GABA levels were estimated for 18 different brain sites. In response to different doses of acute ethanol administration, datasets of 529 rats were analyzed and a non-linear dose response (glutamate and GABA release) relationship was observed in several brain sites. Specifically, glutamate in the nucleus accumbens shows a decreasing logarithmic dose response curve. Finally, regression analysis of 11 published reports employing brain microdialysis experiments in 104 alcohol-dependent rats reveals very consistent augmented extracellular glutamate and GABA levels in various brain sites that correlate with the intensity of the withdrawal response were identified.

**Conclusions:** In summary, our results provide standardized basal values for future experimental and *in silico* studies on neurotransmitter release in the rat brain and may be helpful to understand the effect of ethanol on neurotransmitter release. Furthermore, this study illustrates the benefit of meta-analyses using the generalization of a wide range of preclinical data.

**Keywords:** Microdialysis, Glutamate, GABA, Meta-analysis, Rat brain, Ethanol administration, Alcohol withdrawal

## Background

*In vivo* microdialysis methods have been developed to study the quantity of the chemical composition of interstitial tissue fluids. This technique has been used to observe the extracellular neurotransmitter release in various brain regions of different species. Usually these studies first establish a baseline level of a specific neurotransmitter and

subsequently investigate alterations in extracellular neurotransmitter concentrations in response to the administration of a certain drug or other manipulation.

Numerous microdialysis studies focus on amino acids, in particular glutamate and GABA, as these neurotransmitters are the key players in the excitatory and inhibitory network of the central nervous system (CNS) and are involved in a variety of neuropsychiatric diseases, including substance abuse and alcohol use disorders (Kalivas, 2009; Spanagel, 2009).

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In recent years, the glutamate theory of alcoholism has emerged as a major theory in the addiction research field. In a seminal publication, David Lovinger and colleagues (Lovinger et al. 1989) demonstrated that N-methyl-D-aspartate (NMDA) receptor function was inhibited by ethanol. Further research using site-directed mutagenesis experiments identified putative binding sites for ethanol molecules at the NMDA receptor (for review, see Spanagel, 2009). Thus, the first level of interaction of alcohol with brain function concerns the NMDA receptor (but also the  $\gamma$ -aminobutyric acid A (GABA<sub>A</sub>) receptor and other primary targets of ethanol in the brain; for an overview, see Vengeliene et al., 2008). The NMDA receptor is a ligand-gated ion channel with a heteromeric assembly of NR1, NR2 (A-D), and NR3 subunits, and genetic variants that affect the vulnerability to alcohol dependence within the genes encoding these subunits have been identified (Schumann et al., 2008; Domart et al., 2012; Tsai and Coyle, 2012). In addition to this direct interaction with the NMDA receptor, acute alcohol administration also affects glutamatergic neurons at the synaptic and cellular level and thereby releases glutamate. Although numerous microdialysis studies have examined the alcohol-induced glutamate release process, its concentration-dependency is less clear. It is further proposed that through various neuroadaptive responses that restore homeostasis, chronic alcohol consumption leads to an enhanced activity of the glutamatergic system in alcohol-dependent individuals (Tsai and Coyle, 1998; Spanagel and Kiefer, 2008; Ding et al., 2012). This glutamate-induced hyperexcitability within the CNS is uncovered during alcohol withdrawal. Acute alcohol withdrawal responses, which typically occur after discontinuation of prolonged and excessive alcohol ingestion, are associated with increased central glutamatergic transmission. Several studies employing brain microdialysis experiments in alcohol-dependent animals have shown augmented extracellular glutamate levels in various brain sites that correlate with the intensity of the withdrawal response (Rossetti and Carboni, 1995; Gass and Olive, 2008; Gass et al., 2011). This finding also translates into the human situation, as alcoholics undergoing acute withdrawal exhibit increased glutamate brain levels, as measured by magnetic resonance spectroscopy (Hermann et al., 2012).

As previously mentioned, other receptors or ion channels expressed within the CNS also have putative alcohol binding sites. In particular, the function of GABA<sub>A</sub> receptors is enhanced by ethanol. The GABA<sub>A</sub> receptor/chloride channel complex is a pentameric ligand-gated ion channel and the major inhibitory neurotransmitter receptor in the mammalian brain. Several subunits have been identified, with the majority of GABA<sub>A</sub> receptors

composed of  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  subunits (Barnard et al., 1998; Rewal et al., 2012). Using different receptor constructs, putative ethanol binding sites in the transmembrane domains of the  $\alpha/\beta$  subunits of the GABA<sub>A</sub> receptor have been identified (Mihic et al., 1997), and genetic variants within the genes encoding these subunits have been shown to affect the vulnerability to alcohol dependence (Cui et al., 2012; Frank et al., 2012; Uhart et al., 2012). Finally, some microdialysis studies have shown that acute alcohol also affects GABA release (Koob, 2004). Thus, consistent with the neuroadaptive changes that occur in the glutamatergic system, similar alterations might also occur in the GABAergic system following chronic alcohol administration.

Despite the important advantages of microdialysis measurements, the low spatiotemporal resolution remains a major drawback of these investigations. However, recent studies on the modeling of acute and chronic drug effects (Noori, 2012; Noori et al., 2012a) suggest that *in silico* analysis of the neurochemical processes provides complimentary information to overcome the experimental difficulties, particularly by enabling the observation of the dynamical multi-dimensional interactions of different transmitter systems with high spatiotemporal resolution. These computational methods rely on microdialysis results as initial setup parameters. Thus, comprehensive insights on the dynamical behavior of the extracellular concentrations of these neurochemical systems are of particular importance for understanding the neurobiology of alcohol abuse and alcoholism by conventional or *in silico* approaches. We have introduced a neurocircuitry (Noori et al., 2012a) that provides the foundation of such computational models. Using systematic data mining and clustering methods, we have identified specific brain regions and neurotransmitter systems, including glutamate and GABA, that are critical for understanding the spatiotemporal effects of drugs, especially alcohol, on the neurochemical mechanisms and processes in the rodent brain.

The main objective of the present study is to provide universally valid basal amino acid (glutamate and GABA) concentrations and their alterations due (i) to the administration of acute ethanol and (ii) during withdrawal, as measured by *in vivo* microdialysis experiments. Our previous studies (Frank et al., 2008; Noori et al., 2012b; Brand et al., 2013) suggest that meta regression analysis presents a suitable framework to approach this aim. Here, we use a similar strategy as in these studies and apply equivalent data mining and analytic methods.

Meta-analysis describes the integration of several primary studies using quantitative and statistical methods (Glass, 1976; Smith and Glass, 1977). The

intention is to summarize the results of a large collection of individual studies in order to give a universally valid statement on specific topics. In particular, the effectiveness of a specific treatment or measure is investigated.

## Methods

### Data mining

A literature search was conducted on Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/>). No particular journal was preferred. The search included the specific brain region and the transmitter of interest as well as the keywords “rat” and “microdialysis”. Literature search for ethanol administration also included the keyword “ethanol” and “alcohol”. The selection criteria further included (i) rats of the age between 2 and 15 months and (ii) drug-naïve rats. Articles that did not comply with these criteria had to be excluded. Out of approximately 5000 publications, 245 publications fulfilled the selection criteria. In a second search we included “withdrawal”. Out of 43 publications, 11 publications fulfilled our stringent selection criteria for this additional meta-analysis.

The subsequent variables (i.-vii.) were obtained from the publications and used for further analysis:

- i. Weight, age, gender and consciousness of the rats (if anaesthetics applied: agent and dose).
- ii. Number of the animals used in each experiment.
- iii. Absolute basal glutamate and GABA values.  
Different units were converted into molarity (nM).
- iv. Sample time in min and perfusion rate in  $\mu\text{l}/\text{min}$ .
- v. Peak % baseline (= highest divergence between maximum peak and baseline value) and peak time.
- vi. Coordinates of probe placements according to the stereotaxic atlas of (Paxinos and Watson, 2007), Pellegrino et al. (Pellegrino and Cushman 1979), or König and Klippel (1974) as well as the shape, length and outer diameter of the probe membrane (mm), the calcium concentration and pH value of the Ringer solution or artificial CSF (mM), and the neurochemical detection assays.
- vii. Doses of ethanol applied, as well as the route of administration (intravenous (i.v.) and intraperitoneal (i.p.) injections or local infusions).

### Statistical analysis

Usually a meta-analysis observes an entire experiment. Although we considered only selected values, we did not lose the relation to the experiment in total. The mean basal values are not collected from only one animal that means numbers, percentages etc. are associated to the whole experiment. We conducted the meta-analysis

using fixed effect model (Hedges and Olkin, 1985), which utilizes the inverse of the number of animals of the studies as the weights to calculate a weighted average  $\bar{x} = \frac{1}{N} \sum_{i=1}^k n_i x_i$ , where  $\bar{x}$  represents the weighted average value as the weighted sum of the products of the mean values  $x_i$  from each experiment  $i$  (within a time interval of [0; 300] minutes) and the number of animals used in that particular study  $n_i$ , and  $N = \sum_{i=1}^k n_i$  denoting the total number of animals considered in the meta-analysis of the  $k$  studies. To guarantee the robustness of this model, we have analyzed the datasets statistically with respect to the experimental parameters by one-way analysis of variance (ANOVA) using the Holm-Bonferroni method with a global level of significance of  $\alpha < 0.05$  and identified significant heterogeneity factors.

One purpose of the analysis was to get the mean basal value of the two neurotransmitters glutamate and GABA measured in a defined brain region. According to our defined neurocircuitry for modelling acute and chronic effects of alcohol 19 brain regions were taken into consideration - from caudal to rostral: olfactory bulb (OB), prefrontal cortex (PFC), insula (Ins), nucleus accumbens (NAc), caudate putamen (CPu), septal region (S), bed nucleus of stria terminalis (BNST), globus pallidus (GP), hypothalamus (HyT), amygdala (Amy), habenula (Hb), hippocampus (Hc), thalamus (Th), subthalamic nucleus (STh), substantia nigra (SN), ventral tegmental area (VTA), raphe nuclei (R), locus coeruleus (LC), and pons (Pn). As mentioned above, weighted values (concerning the number of rats, which were taken in one experiment) were used for calculation in order to get an average basal value. In addition to systematically examine those baseline values the second objective was the “peak % baseline” after acute administration of alcohol (i.p., i.v., s.c., local). A dose-dependent correlation analysis was conducted using the variables peak % baseline, peak time and the given dose of ethanol to determine the functional relationship between administered dose of ethanol and the alteration of glutamate and GABA concentrations, respectively. The third objective was the estimation of “peak % baseline” and “peak time” during alcohol withdrawal.

To analyse the data, one-way analysis of variance (ANOVA) using Holm-Bonferroni method with a global level of significance of  $\alpha < 0.05$  were performed. If any significance emerged, the respective weighted average basal value and standard error were calculated separately. Additionally forest plots were used to illustrate the influence of ethanol on the baseline values of glutamate in the prefrontal cortex and the nucleus accumbens. This graphical representation is a scattergram of the variables “experiment” and “average basal value” and “peak % baseline”, respectively.

## Results

### Baseline values for extracellular glutamate and GABA concentrations in different areas of the rat brain

Literature search revealed 245 publications that fulfilled the selection criteria for baseline values of glutamate and GABA. Out of these 43.3% were published before the year 2000, 51.8% between 2000 and 2010 and 4.5% after 2010. Altogether 6932 animals were used in these experiments. Average basal values, as well as the statistical distribution (i.e., median, maximum and minimum) are represented in Table 1 (glutamate) and Table 2 (GABA) for 18 different brain regions respectively (for the habenula no data could be retrieved from Pubmed). The forest plots (Figures 1 and 2) represent the basal values of glutamate in the PFC and the NAC, respectively. Rapid microelectrode measurements of glutamate in the PFC (Hascup et al., 2010), glutamate measurements with oxidase-coated biosensors in the AMY and NAC (Gass et al., 2011) as well as a variety of control experiments (Timmerman and Westerink, 1997; Sun et al., 2011) suggest the neuronal origin of these concentrations.

Numerous experimental variables are known to have an impact on the relative recovery of an analyte and thereby influence the concentration per sample and the baseline values measured. Most critical parameters are the flow rate of the perfusate, probe size, the composition of the perfusate - particularly the  $\text{Ca}^{2+}$  concentration, and the analytical technique for determining the neurotransmitter concentrations. The statistical distribution of these parameters within our datasets (Table 3) suggests a dense distribution of the parameters around their averages and a lack of significant heterogeneity in the applied ranges. ANOVA performed on the weighted averages with respect to these parameters reflected this absence of variance and suggests the robustness of our analysis in agreement with previous studies (Frank et al., 2008; Noori et al., 2012b; Brand et al., 2013). This result is not in contrast to the previous experimental observation but underlines the awareness of the study designers of the importance of these parameters. This was particularly reflected in the choice of the shape of the probes (99% I-shaped) and the transmitter detection systems. Almost all studies (98%) used high performance liquid chromatography (HPLC) and fluorescence detection systems for glutamate quantifications, whereas the vast majority of the studies measuring GABA utilize HPLC and coulometric electrochemical detection assays. However, it should also be mentioned that the majority of the studies used in the present study did not report the time point of measurement with respect to circadian rhythms. Recent studies (Castaneda et al., 2004; Hampp et al., 2008) suggest that the neurotransmitter levels measured by *in vivo* microdialysis are under the

control of the circadian clock and vary with the time of the day. The lack of information on this issue in most of the publications might have a non-negligible impact on our analysis.

Most of the experiments used Sprague–Dawley (43.4%) and Wistar rats (42.3%). A smaller percentage used Lister-Hooded (2.4%) and Long-Evans (3.1%) rats. Statistical analysis shows statistically significant differences of average basal values of rat strain in several brain regions. Most of them occurred between Wistar and Sprague–Dawley rats (strain differences shown in Table 1 and 2). In particular, GABA levels in the PFC and CPu were significantly different between Sprague–Dawley and Wistar rats ( $F_{1,6} = 6.03$ ; resp.  $F_{1,10} = 4.76$ ;  $P < 0.05$ ). Furthermore, glutamate levels showed a statistically significant difference between Sprague–Dawley and Wistar rats in the GP ( $F_{1,5} = 9.11$ ;  $p < 0.05$ ), the SN ( $F_{1,9} = 4.67$ ;  $P < 0.05$ ), and the VTA ( $F_{2,8} = 4.26$ ;  $P < 0.05$ ). In general, the average basal values seem not to depend on gender. However, with the exception of measurements in the OB, which were performed only on female animals ( $n = 100$ ), the majority of the remaining studies (96.5%) used male rats. Hence, statistical analysis did not reveal any gender-specific significant differences, but due to the low number of female rats it is difficult to draw any certain conclusion. In order to minimize age-related variations, only values obtained from adult animals (between 2 and 10 months of age) were considered for the analysis. The weight of the animals was Gaussian normal distributed around 300 g. The dominant part of the experiments (78%) was conducted on awake, conscious and freely moving animals. In the remaining studies, animals were maintained under anaesthesia during the experiment, which often induced statistically significant effects on the basal neurotransmitter concentrations (Table 4). Previous studies (Lillrank et al., 1994; Rozza et al., 2000; Dong et al., 2006; Westphalen and Hemmings, 2006) already suggest a significant impact of the anaesthetics on the forebrain glutamate and GABA levels. Our analysis further supports the suggestion that the application of different anaesthetics such as halothane, urethane and pentobarbital increase the level of glutamate significantly in Th ( $F_{1,6} = 80.12$ ;  $P < 0.05$ ), SN ( $F_{1,14} = 6.3$ ;  $P < 0.05$ ), and VTA ( $F_{1,10} = 83.53$ ;  $P < 0.05$ ). In addition, chloral hydrate appeared to also have enhancing effects on the GABA release in the SN ( $F_{1,4} = 216.28$ ;  $P < 0.05$ ) (Table 4).

### Alcohol-induced glutamate and GABA release in different areas of the rat brain

Our literature search revealed 17 publications that were in agreement with our selection criteria for acute ethanol exposure. Out of these, 66 values were extracted. Altogether 529 animals were used in the experiments. Observation of seven brain regions fulfilled the selection



**Table 1 Average basal values (nM) of glutamate in awake animals as well as the statistical distribution of the data (i.e., median, maximum and minimum)**

Brain region (Number of rats)	Glutamate: average basal value $\pm$ sEM [nM]	Median	Max	Min
<b>Olfactory Bulb</b> (30)	3857 $\pm$ 2057	4681	3307	6055
<b>Prefrontal Cortex</b> (445)	1182 $\pm$ 236	1290	3500	105
<b>Insular Cortex</b> (6)	1750 $\pm$ 320	-	-	-
<b>Nucleus Accumbens</b> (661)	2135 $\pm$ 382	623	12379	10
<b>Caudate Putamen</b> (675)	1009 $\pm$ 166	735	8100	25
<b>Bed Nucleus of Stria Terminalis</b> (7)	830 $\pm$ 70	-	-	-
<b>Globus Pallidus</b>	435 $\pm$ 153	400	673	171
Sprague–Dawley (42)				
Wistar (39)	876 $\pm$ 381	1518	1905	236
<b>Hypothalamus</b> (63)	1178 $\pm$ 373	492	3500	24
<b>Amygdala</b> (138)	4475 $\pm$ 1779	835	10980	32
<b>Hippocampus</b> (301)	2616 $\pm$ 513	1480	18940	50
<b>Thalamus</b> (71)	842 $\pm$ 280	705	1640	114
<b>Subthalamic Nucleus</b> (30)	118 $\pm$ 1	-	-	-
<b>Substantia Nigra</b> Sprague–Dawley (487)	136 $\pm$ 41	115	518	88
Wistar (75)	517 $\pm$ 210	500	684	110
<b>Ventral Tegmental Area</b>	205 $\pm$ 68	177	410	114
Sprague–Dawley (184)				
Wistar (17)	571 $\pm$ 342	504	733	275
Long-Evans (59)	1294 $\pm$ 654	1295	1489	1100
<b>Raphe</b> (7)	1243 $\pm$ 92	-	-	-
<b>Locus Coeruleus</b> (100)	2430 $\pm$ 730	4400	10750	58
<b>Pons</b> (26)	75 $\pm$ 5	-	-	-

**OB:** Guevara-Guzman, R., et al. (2000) **PFC:** Abekawa et al. (2006); Ballini et al. (2008); Calcagno et al. (2006); Carli et al. (2011); Del Arco and Mora (1999); Del Arco and Mora (2000); Del Arco and Mora (2002); Giovannini et al. (2005); Harte and O'Connor (2004); Hashimoto et al. (1995); Hernandez et al. (2008); Huang et al. (2008); Hugues et al. (2007); Li et al. (2010b); Lupinsky et al. (2010); Ohoyama et al. (2011); Pistis et al. (2002); Qi et al. (2012); Robert et al. (1996); Selim and Bradberry (1996); Stephans and Yamamoto (1995); Timmerman et al. (1999); Welty and Shoblock (2009); Yamamura et al. (2009a) **Ins:** Guzman-Ramos et al. (2010) **NAC:** Dahchour et al. (1996); Dalley et al. (1999); Dawson et al. (2001); Ericson et al., (2011); Fu et al. (2000); Giorgetti et al. (2001); Hemmati et al. (2001); Hernandez et al. (2008); Hotsenpiller and Wolf (2003); Huang et al. (2008); Ito, et al. (2006); Lallemand et al. (2006); Li et al.(2010a); Mikhailova (2003); Quarta et al. (2004); Quertemont et al.(2000); Saulskaya and Mikhailova (2002); Saul'skaya and Mikhailova (2005); Saulskaya and Soloviova (2004); Segovia et al. (1999); Selim and Bradberry (1996); Shou et al. (2004); Xi et al. (2003b); You et al. (2001); You et al. (1998); Zangen and Hyodo (2002) **CPu:** Anderson and DiMicco (1992); Battaglia et al. (1997); Bert et al. (2002); Carboni et al. (1993); Dawson et al. (2001); Dawson et al. (2003); Del Arco et al. (1998); Fantin et al. (2007); Ferraro et al. (1998); Hashimoto et al. (1995); Hernandez et al. (2008); Lillrank et al. (1994); Mark et al. (2004); Massieu et al. (1995); Meeusen et al. (1997); Melani et al. (2003); Molchanova et al. (2004a); Molchanova, et al. (2004b); Morales-Villagran and Tapia (1996); Morari et al. (1996); Morari et al. (1993); Morari (1994); Northrop et al. (2011); Parrot et al. (2003); Segovia et al. (1997); Segovia et al. (1999); Segovia et al. (2001); Stephans and Yamamoto (1995); Takeda et al. (2003); Toth et al. (1993); Yamada et al. (2009); Yamamoto et al. (1999) **BST:** Forray et al. (1999) **GP:** Biggs et al. (1997a); Biggs and Starr (1997b); Chapman and See (1996); Fantin et al. (2007); Ferraro et al. (1998); Galeffi et al. (2003); Kretschmer (2000); Li et al. (2010a); Sizemore et al. (2000); Windels et al. (2000); Windels et al. (2005) **HyT:** Anderson and DiMicco (1992); Azuma et al. (1996); Ferraro et al. (1999); Keck et al. (2000); Mason et al. (1997); Melis et al. (2004); Succu et al. (2006) **Amy:** Kaura et al. (1995); Mucignat-Caretta et al. (2006); Quertemont et al. (1999); Quertemont et al. (1998); Roberto et al. (2004b); Skorzevska et al. (2009) **Hc:** Ballini et al. (2008); Biggs et al. (1992); Clinckers et al. (2005); Dawson et al. (2001); Ferraro et al. (1997a); Giovannini et al. (2005); Giovannini et al. (2001); Giovannini et al. (1998); Hossain et al. (2008); Katoh et al. (1997); Kuntz et al. (2004); Langlais and Zhang (1993); Oreiro-Garcia et al. (2007); Rakovska et al. (1998); Rosi et al. (2004); Rowley et al. (1995); Shimizu et al. (1998); Takeda et al. (2004); Takeda et al. (2002); Tanaka et al. (2004); Ueda and Tsuru (1995); Wislowska-Stanek et al. (2008); Zhu et al. (2008); Zuiderwijk et al. (1996) **Th:** Abarca et al. (2000); Banerjee and Snead (1995); Ferraro et al. (1997b); Hazell et al. (1993); Langlais and Zhang (1993); Nyitrai et al. (1999); Terzioglu et al. (2006) **STh:** Ampe et al. (2007) **SN:** Bianchi et al. (1998); Biggs et al. (1995); Boulet et al. (2006); Fantin et al. (2007); Ferraro et al. (1998); Ferraro et al. (2001); Galeffi et al. (2003); Hatzipetros and Yamamoto (2006); Marti et al. (2002); Morari et al. (1998); Nyitrai et al. (1999); Robelet et al. (2004); Rosales et al. (1997); Yamamura et al. (2009ba) **VTA:** Frantz et al. (2002); Fu et al. (2000); Harte and O'Connor (2004) Harte and O'Connor (2005); Kretschmer et al. (2000); O'Dell (2004); Pehek et al. (2006); Timmerman et al. (1999); Wang et al. (2005); Wolf and Xue (1998); Wolf and Xue (1999); You et al. (2007) **R:** Varga et al. (1998) **LC:** Feng et al. (1997); Feng et al. (1995); Hoshi et al. (1996); Hoshi et al. (1997); Liu et al. (1999); Singewald et al. (1995); Sullivan et al. (2000); Timmerman, et al. (1999); Tokuyama et al. (1998); Zhang et al. (1994) **Pn:** Sato et al. (2007).

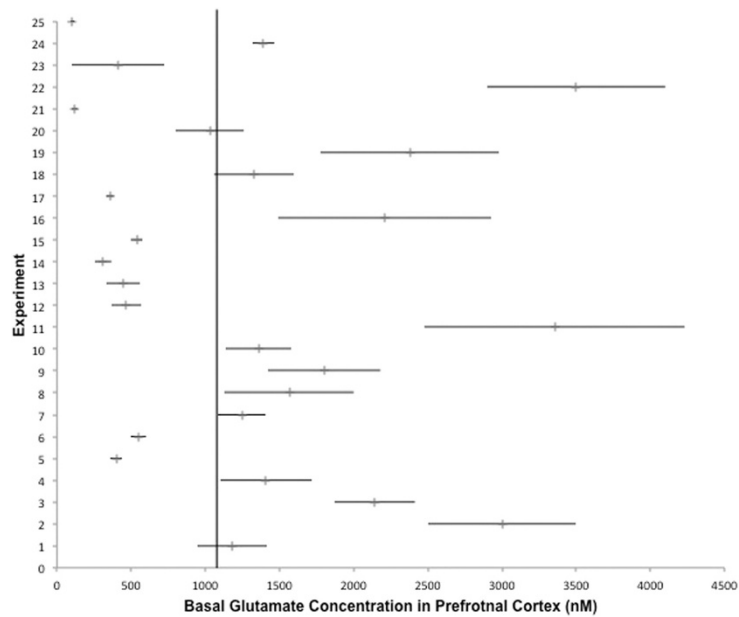
criteria: AMY, GP, HC, NAc, PFC, CPu, and VTA. In general, alcohol was administered via three routes: (i) almost 90% of the experiments used intraperitoneal (i.p.) injections in a dose between 0.5 and 3.0 g/kg body weight; (ii) local infusion (100–1000 mM) of alcohol in 8% of the studies; and (iii) the remaining experiments applied ethanol orally (20% ethanol). The average magnitude of increase/decrease comparing to the baseline

concentrations (peak % baseline) and the average peak time are presented in the Tables 5 and 6. The correlation analysis shows a non-uniform (region-dependent) interaction between ethanol and the release of glutamate and GABA. In particular, ethanol-induced alterations in glutamate concentrations appear to depend on the network properties such as the connectivity of the brain regions within the neurocircuitry for modelling drug effects.

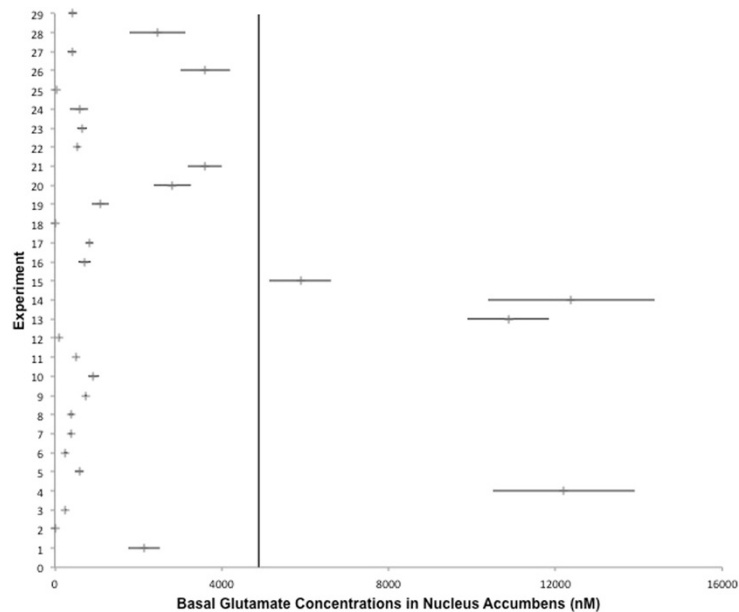
**Table 2 Average basal values (nM) of GABA in awake animals as well as the statistical distribution of the data (i.e. median, maximum and minimum)**

Brain region (Number of rats)	GABA: average basal value $\pm$ SEM [nM]	Median	Max	Min
<b>Olfactory Bulb</b> (30)	73 $\pm$ 46	61	80	43
<b>Prefrontal Cortex</b> Sprague–Dawley (131)	34 $\pm$ 12	32	50	25
Wistar (80)	89 $\pm$ 33	118	170	10
<b>Nucleus Accumbens</b> (167)	90 $\pm$ 22	33	764	13
<b>Caudate Putamen</b> Sprague–Dawley (341)	17 $\pm$ 5	19	130	6
Wistar (300)	78 $\pm$ 22	110	660	1
<b>Septal Region</b> (17)	640 $\pm$ 420	488	775	200
<b>Bed Nucleus of Stria Terminalis</b> (7)	110 $\pm$ 20	-	-	-
<b>Globus Pallidus</b> (198)	21 $\pm$ 6	19	83	7
<b>Hypothalamus</b> (56)	29 $\pm$ 10	17	92	5
<b>Amygdala</b> (128)	56 $\pm$ 20	16	830	2
<b>Hippocampus</b> (302)	97 $\pm$ 19	95	2500	1
<b>Thalamus</b> (100)	228 $\pm$ 70	60	870	8
<b>Subthalamic Nucleus</b> (33)	9 $\pm$ 5	9	9	9
<b>Substantia Nigra</b> (454)	18 $\pm$ 4	15	145	4
<b>Ventral Tegmental Area</b> (202)	16 $\pm$ 6	23	43	8
<b>Locus Coeruleus</b> (6)	6 $\pm$ 1	-	-	-
<b>Pons</b> (26)	90 $\pm$ 7	-	-	-

**OB:** Guevara-Guzman et al. (2000) **PFC:** Ballini et al. (2008); Del Arco and Mora (1999); Del Arco and Mora (2000); Del Arco and Mora (2002); Grobin and Deutch (1998); Harte and O'Connor (2004); Hernandez et al. (2008); Huang et al. (2008); Ohoyama et al. (2011); Petkova-Kirova et al. (2008) Pistis et al. (2002); Welty and Shoblock (2009); Yamamura et al. (2009a) **NAc:** Dahchour (1996); Ferraro et al. (1996a); Hazell (1993); Hemmati et al. (2001); Hernandez (2008); Huang et al. (2008); Lindfors et al. (1992); Reynolds et al. (1999); Segovia (1999); Shou et al. (2004); Smith and Sharp (1994); Tanganelli et al. (1994); Xi et al. (2003a) **CPu:** Anderson and DiMicco (1992); Bourdelais and Deutch (1994); Del Arco et al. (1998); Fantin et al. (2007); Ferraro et al. (1998); Ferraro et al. (1997b); Hernandez et al. (2003); Hernandez et al. (2008); Hondo et al. (1995); Lillrank et al. (1994); Meeusen et al. (1997); Melani et al. (2003); Molchanova et al. (2004a); Morari et al. (1996); Morari et al. (1993); Morari et al. (1994); Segovia et al. (1997); Segovia et al. (1999); Semba et al. (1995); Takeda et al. (2003); Wang et al. (2007); Yamamoto et al. (1999) **S:** Giovannini et al. (1994); Sotomayor-Zarate et al. (2010) **BST:** Forray et al. (1999) **GP:** Chapman and See, (1996) Cowen et al. (1998); Fantin et al. (2007); Ferraro et al. (1998); Ferraro et al. (1997a); Ferraro et al. (2000); Galeffi et al. (2003); Inui et al. (2009); Littlewood et al. (2006); O'Connor et al. (1998); Rimondini et al. (1994); Rimondini et al. (1996); Sizemore et al. (2000); Sommer et al. (1996); Windels et al. (2000); Windels et al. (2005) **Hyt:** Anderson and DiMicco (1992); Dong et al. (2006); Ferraro et al. (1999); Ferraro et al. (1996b); Katoh et al. (1997); Voisin et al. (1994) **Amy:** Kaura et al. (1995); Mucignat-Caretta et al. (2006); Quertemont et al. (1999); Rea et al. (2009); Roberto et al. (2010); Roberto et al. (2004b); Skorzevska et al. (2009) **HC:** Ballini et al. (2008); Biggs et al. (1992); Dalby (2000); de Groote and Linthorst (2007); Ferraro et al. (1997b); Giovannini et al. (2001); Giovannini et al. (1998); Hossain et al. (2008); Katoh et al. (1997); Kuntz et al. (2004); Langlais and Zhang (1993); Oreiro-Garcia et al. (2007); Rakovska et al. (1998); Rosi et al. (2004); Rowley et al. (1995); Takeda et al. (2004); Takeda et al. (2002); Ueda and Tsuru (1995); Wislowska-Stanek et al. (2008); Yoshida et al. (2007); Zuiderwijk et al. (1996) **Th:** Banerjee and Snead (1995); Dalby (2000); Ferraro et al. (1996b); Ferraro et al. (2001); Juhasz et al. (1997); Langlais and Zhang (1993); Mark (2004); Nyitrai et al. (1999); Terzioglu et al. (2006) **STh:** Ampe et al. (2007); Yamamura et al. (2009a) **SN:** Bianchi et al. (1998); Biggs et al. (1995); Boulet et al. (2006); Bustamante et al. (2002); Fantin et al. (2007); Ferraro et al. (1998); Ferraro et al. (2001); Galeffi et al. (2003); Herrera-Marschitz et al. (1996); Invernizzi et al. (2007); Mark et al. (2004); Matuszewich and Yamamoto (1999); Morari et al. (1996); Ochi et al. (2004); Rosales et al. (1997); Sayin et al. (1995); Sommer et al. (1996); Windels et al. (2000); Windels et al. (2005); You et al. (1996a); You et al. (1996b); You et al. (2007) **VTA:** Bankson and Yamamoto (2004); Frantz et al. (2002); Harte and O'Connor (2004); O'Dell and Parsons (2004); Winter et al. (2008); Yan et al. (2005); You et al. (2007) **LC:** Singewald et al. (1995) **Pn:** Sato et al. (2007).



**Figure 1 Forest-plot of the basal glutamate values in the prefrontal cortex as measured in 24 experiments, ordered by year of publication.** Row 1 indicates the weighted average basal value and its standard error of mean ( $\pm$ SEM). The vertical line extends the weighted mean in order to compare the extracted data. 2 Hashimoto et al. (1995); 3 Stephans and Yamamoto (1995); 4 Robert et al. (1996); 5,6 Selim and Bradberry (1996); 7 Del Arco and Mora (1999); 8 Timmerman et al. (1999); 9 Del Arco and Mora (2000); 10 Del Arco and Mora (2002); 11 Pistis et al. (2002); 12 Harte and O'Connor (2004); 13 Giovannini et al. (2005); 14 Abekawa et al. (2006); 15 Calcagno et al. (2006); 16 Hugues et al. (2007); 17 Ballini et al. (2008); 18 Hernandez et al. (2008); 19 Huang et al. (2008); 20 Welty and Shoblock (2009); 21 Yamamura et al. (2009a); 22 Li et al. (2010a); 23 Lupinsky et al. (2010); 24 Carli et al. (2011); 25 Ohoyama et al. (2011).



**Figure 2 Forest-plot of the basal value of glutamate in the nucleus accumbens as measured in 28 experiments, ordered by year of publication.** Row 1 indicates the weighted average basal value and its standard error of mean ( $\pm$ SEM). The vertical line extends the weighted mean in order to compare the extracted data. 2 Dahchour et al. (1994); 3 Selim and Bradberry (1996); 4 You et al. (1998); 5 Dalley et al. (1999); 6,7,8 Segovia et al. (1999); 9 Fu et al. (2000); 10 Quertemont et al. (2000); 11 Dawson et al. (2001); 12 Giorgetti et al. (2001); 13,14 Hemmati et al. (2001); 15 You et al. (2001); 16 Saulskaya and Mikhailova (2002); 17 Zangen and Hyodo (2002); 18 Hotsenpiller and Wolf (2003); 19 Mikhailova (2003); 20 Xi et al. (2003a); 21 Quarta et al. (2004); 22 Saulskaya and Soloviova (2004); 23 Shou et al. (2004); 24 Saul'skaya and Mikhailova (2005); 25 Ito et al. (2006); 26 Lallemand et al. (2006); 27 Hernandez (2008); 28 Huang et al. (2008); 29 Li et al. (2010b).

**Table 3 Statistical distribution of the microdialysis procedure parameters within the meta-analyzed datasets**

	Average	Median	Max	Min
<b>Flow Rate (µl/min)</b>	1.7	2.0	4.0	0.5
<b>Ca<sup>2+</sup> (mM)</b>				
aCSF (53%)	1.2	1.2	2.5	0.57
Ringer Solution (30%)	1.9	2.2	3.4	1.0
Krebs-Ringer-Phosphate Solution (9%)	1.5	1.2	3.4	1.0
Modified Ringer Solution (7%)	1.4	1.2	2.3	1.0
Dulbecco Phosphate Buffer Saline (1%)	1.2	1.2	1.2	1.2
<b>pH-value (Perfusate)</b>	7.4	7.4	7.4	6.0
<b>Probe Size</b>				
Length (mm)	2.3	2.0	5.0	1.0
Outer Diameter (mm)	0.3	0.3	0.6	0.15

The compliance of the average values and the median in the flow rates and in the different calcium concentrations within the composition of perfusates suggest a lack of heterogeneity and a high level of standardization in the general experimental design of microdialysis measurements.

**Table 4 Significantly different average basal values (nM) of glutamate and GABA (in comparison to Tables 1 and 2) in anesthetized rats**

Brain region/ transmitter (number of animals)	Average basal value ± SEM	Median	Max	Min
Thalamus/Glu (8)	6600 ± 300	-	-	-
Substantia Nigra/Glu (16)	684 ± 259	699	863	440
Ventral Tegmental Area/Glu (12)	4607 ± 392	-	-	-
Ventral Tegmental Area/GABA (6)	226 ± 79	-	-	-

**Glu-Th:** Juhasz et al. (1997) **Glu-SN:** Bustamante et al. (2002); Herrera-Marschitz et al. (1996); Windels et al. (2000); Windels et al. (2005); You, et al. (1996a); You et al. (1996b) **Glu-VTA:** You et al. (2001) **GABA-VTA:** Winter et al. (2008).

**Table 5 Average ethanol-induced alterations of glutamate and GABA as measured by *in vivo* microdialysis experiments**

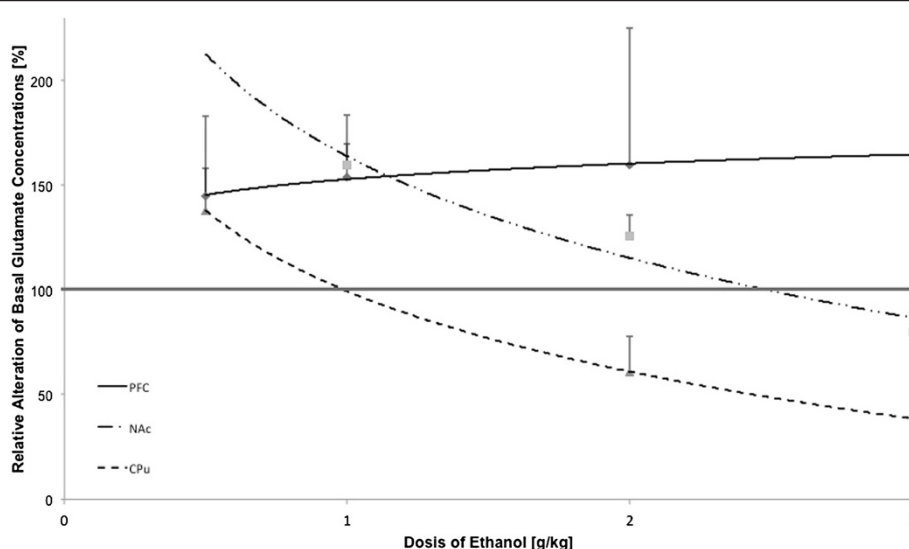
EtOH dosis (g/kg)	0.5	1.0	2.0	3.0
	Peak % baseline (Peak time [min])			
<b>Brain region/transmitter (number of animals)</b>				
Prefrontal Cortex/Glu (44)	145 (40)	154 (57)	160 (20)	
Nucleus Accumbens/Glu (186)		160 (53)	126 (49)	80 (80)
Nucleus Accumbens/GABA (82)		135 (58)	97 (65)	73 (90)
Caudate Putamen/Glu (11)	138 (NN)		61 (20)	

**Glu-PFC:** Selim and Bradberry (1996); **Glu-NAc:** Dahchour et al. (1994); Dahchour et al. (1996); Kashkin and De Witte (2004); Selim and Bradberry (1996); Yan et al. (1998) **GABA-NAc:** Dahchour et al. (1994); Dahchour et al. (1996); **Glu-CPu:** Carboni et al. (1993); Smith et al. (2004).

**Table 6 Local infusion of ethanol in the AMY enhances GABA levels significantly, while glutamate release remains almost unchanged (Glu: Roberto et al. (2004b) GABA: Roberto et al. (2004a))**

EtOH dosis (mM)	100	300	1000
	Peak % Baseline		
<b>Amygdala/Glu</b>	110	104	113
<b>Amygdala/GABA</b>	127	-	182





**Figure 3** Dose-dependent ethanol induced changes of extracellular glutamate concentrations (nM) in the prefrontal cortex (PFC), nucleus accumbens (NAc) and caudate putamen (CPu) of rats.

This observation is best reflected in the analysis of the PFC, NAc and CPu (Figure 3). While ethanol increases the glutamate concentrations in the PFC in a dose-dependent fashion, it simultaneously decreases the extracellular levels of glutamate in the NAc and CPu. In contrast GABA concentrations were elevated in the NAc following the same doses of alcohol.

#### Alcohol withdrawal-induced glutamate and GABA release in different areas of the rat brain

On the basis of our selection criteria for ethanol withdrawal, 11 articles (n = 104 rats) were extracted. All studies used freely moving male rats with a strain distribution of 55% Wistar and 45% Sprague Dawley animals. The experiments measured the amino acids alterations in an interval of [2; 12] hours after last exposure to

alcohol within different brain regions (Table 7 and Figure 4) with significant enhancements of extracellular glutamate and GABA levels due to acute ethanol withdrawal.

#### Discussion

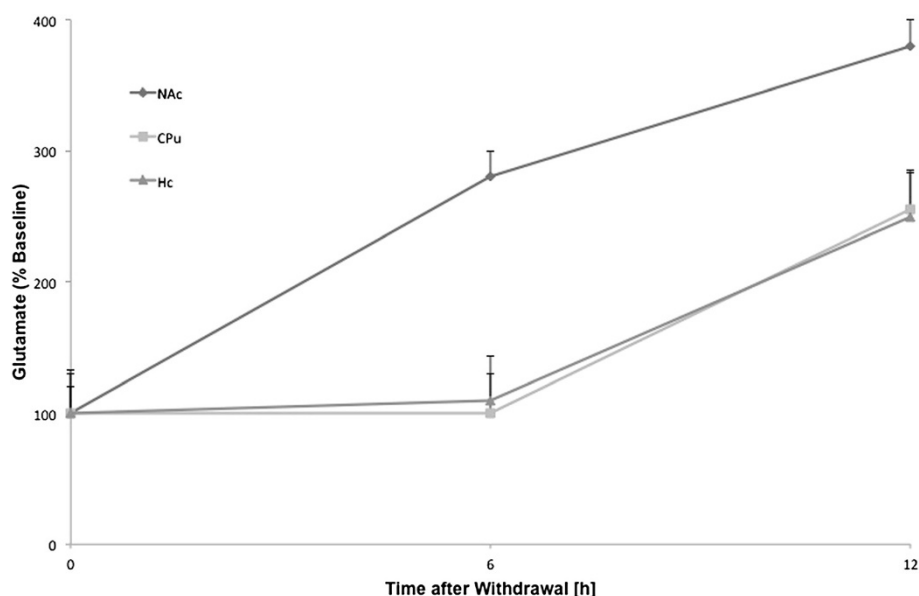
To investigate the effects of a specific drug on amino acid release in the rat brain, *in vivo* microdialysis is an ideal method. Nevertheless, experimental parameters should be defined more precisely, as they can largely vary between different publications; however, there are no universal instructions concerning the number of animals, gender, age, doses of applied drugs, state of consciousness and weight in these studies. Our meta-analysis shows general robustness of the observations for glutamate and GABA release with respect to experimental parameters such as gender and state of consciousness of the animals, and provides universal references for the basal concentrations of glutamate and GABA in a number of brain regions. However, the observed statistical differences of glutamate and GABA neurotransmission in specific brain regions as a consequence of the administration of anaesthetics and strain of the animals suggest particular cautiousness in establishing baseline measurements with respect to these variables.

Our analysis further reflects the highly complex mechanisms underlying the actions of ethanol on the release properties of amino acids. While different doses of ethanol enhance the basal levels of glutamate in the PFC (Table 4 and Figure 3), the magnitude of the alterations appear to be nonlinearly dependent on the applied

**Table 7** The effects of acute ethanol withdrawal on extracellular amino acid concentrations in rats

Brain Region (Number of rats)	Glutamate	GABA
Central Amygdala (21)	216%	360%
Nucleus Accumbens (39)	370%	
Caudate Putamen (13)	255%	
Hippocampus (31)	240%	100%

**Glu-Central AMY:** Roberto et al., 2004b; **GABA-Central AMY:** Roberto et al., 2004a, Roberto et al. 2010; **Glu-NAc:** Dahchour et al., 1998; Dahchour and De Witte 1999b, 2000, 2000; Melendez et al., 2005; Saellstroem Baum et al. 2006; **Glu-CPu:** Rossetti and Carboni, 1995; **Glu-HC:** Dahchour and De Witte, 1999a, 2003; **GABA-HC:** Dahchour and De Witte, 1999a, 2003.



**Figure 4** The time course of withdrawal induced enhancements in the glutamate levels relative to the respective basal values in nucleus accumbens, caudate putamen and hippocampus. The time course was not provided for central amygdala.

doses. In addition, the negative correlation of the administered doses of ethanol and the changes in amino acid concentrations in the dorsal and ventral striatum suggest the involvement of feedback mechanisms and the activation of additional secondary regulatory processes in the subcortical brain structures by alcohol (Noori et al., 2012a).

In general, the multi-scale involvement of glutamate and GABA in information processing in the brain (from synaptic to network interactions) and the interactions between these transmitters make it difficult to identify the key components of the ethanol-induced alterations. In light of these difficulties, *in silico* experiments might represent an alternative strategy to capture the dynamical complexity of these interactions and provide further neurobiological insights on the relevant processes that are not measurable simultaneously in real-world experiments.

## Conclusion

In conclusion, this meta-analysis approach may be helpful for the optimal systematic design of future *in vivo* microdialysis and *in silico* experiments on neurotransmitter release and ethanol-related processes, to therefore attain a better comparability between those studies. Furthermore, the basal extracellular concentrations of glutamate and GABA in 18 different brain sites, as well as the quantitative and qualitative measures for the acute action of ethanol on these neurotransmitters provide the necessary setup parameters for *in silico* studies.

## Limitations

Despite the numerous advantages of meta-analysis approaches, their main problem remains the lack of essential information in the publications. Many potentially important articles had to be excluded from our analysis because crucial information was missing, such as the number of animals used or standard errors of the mean. In addition, it should be noted that in the majority of studies, circadian rhythmicity was not considered and thus the time point of the measurement was oftentimes excluded. Recent studies (Casteneda et al., 2004; Hampp et al., 2008) indicate that there is a relationship between the concentrations of neurotransmitters, as measured by *in vivo* microdialysis, and the time of measurement (day/night).

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

SF, IB and HRN carried out the data mining and statistical analysis and drafted the manuscript. RS and HRN designed the study and wrote the manuscript. All authors read and approved the final manuscript.

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