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LOWER [\(^3\)H]CITALOPRAM BINDING IN BRAIN AREAS RELATED TO SOCIAL COGNITION IN ALCOHOLICS

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Running title: Lower [\(^3\)H]citalopram binding in alcoholics

Key words: serotonin transporters, insula, posterior cingulate cortex, parahippocampal gyrus, whole-hemisphere autoradiography
ABSTRACT

**Aims:** In the present study, putative alterations in the serotonin transporter density were evaluated in anterior and posterior insula, posterior cingulate cortex, dorsolateral and dorsomedial prefrontal cortex, hippocampus, parahippocampal gyrus and dorsal raphe nucleus in Cloninger type 1 (n=9) and type 2 (n=8) alcoholics and non-alcoholic controls (n=10). **Methods:** Human whole-hemisphere autoradiography was used to measure \[^3\text{H}\]citalopram binding to serotonin transporters in eight brain areas in all post-mortem brains. **Results:** Significant differences were observed in the mean \[^3\text{H}\]citalopram binding between the study groups, with antisocial type 2 alcoholics showing the lowest binding. Differences between the study groups were prominent in the posterior insula and posterior cingulate cortex, where both alcoholic groups had low \[^3\text{H}\]citalopram binding, and in the parahippocampal gyrus were only antisocial type 2 alcoholics had low \[^3\text{H}\]citalopram binding when compared to non-alcoholic controls. **Conclusion:** Although these data are preliminary, and from relatively small diagnostic groups, these results show that alcoholics may have lower serotonergic tone in the brain, thus decreasing social cognition and increasing alcohol-cue reactivity.
INTRODUCTION

Alcohol consumption is one of the leading risk factors for disease worldwide, and alcohol has been considered one of the most harmful substances of abuse to both society and individuals, who consume excessive amounts of alcohol (Nutt et al. 2010, Lim et al. 2012). Alcoholics are a heterogeneous group, yet Cloninger’s typology of alcoholism remains a relatively simple way to divide alcoholics into two subgroups (Cloninger 1987). Alcoholism typically starts at an early age (<25 years) for impulsive and antisocial type 2 alcoholics, compared to late onset alcoholism (>25 years) for the socially dependent and anxiety prone type 1 alcoholics. Serotonergic function has an important role in social interactions, which seems to be impaired in alcoholics (Cloninger 1995, Berglund et al. 2013).

Recent human neuroimaging studies have associated additional brain areas with alcohol dependence and alcohol-cue reactivity (Jasinska et al. 2014). These areas include the insular cortex, which has a role in interoception and emotion recognition (Naqvi et al. 2007, Paulus and Stewart 2014); posterior cingulate cortex (PCC), which has been associated with social cognition (Garavan et al. 2000, Brewer et al. 2013); dorsolateral and dorsomedial prefrontal cortices (DLPFC and DMPFC, respectively), which have function in self-regulation and impulse control (Hare et al. 2009, da Silva et al. 2013, Regenbogen et al. 2013, Bruhl et al. 2014); and both hippocampus (HIPP) and parahippocampal gyrus (PHG), which are associated with memory and context recognition processes (Mizumori 2013, Shi et al. 2013, Silk et al. 2013, Zorumski et al. 2014).

Cloninger’s original hypothesis states that type 1 alcoholics have dopaminergic deficiency, whereas type 2 alcoholics have serotonergic deficiencies (Cloninger 1987). The association between type 1 alcoholics and dopamine seems to be true (Tupala and Tiibonen 2004), whereas
demonstrating putative serotonergic deficiencies has been more challenging (Leggio and Addolorato 2008). Both alcoholic groups seem to have decreased serotonin transporter (SERT) densities in the anterior cingulate cortex (ACC) (Mantere et al. 2002), caudate nucleus (Storvik et al. 2006a) and amygdala (Storvik et al. 2007), which suggests that decreased SERT levels could be a common finding for alcoholism as a whole, and not specific for type 2 alcoholics. However, to our knowledge, SERT densities have not been measured in type 1 and 2 alcoholics in the insula, PCC, DLPFC, DMPFC, HIPP or PHG.

There are apparent connectivity differences between the anterior and posterior insula (AINS and PINS, respectively) (Cauda et al. 2012, Chang et al. 2013, Sullivan et al. 2013), which implies that they should be measured separately. Moreover, the dorsal raphe nucleus (DR) is an important serotonergic region, and interactions between DR, cortex and striatum have been associated with reward-seeking behavior and harm avoidance (Cloninger 1987, Celada et al. 2013, Nakamura 2013).

In the present study, $[^3]$H)citalopram was used to measure SERT binding density in post-mortem brain samples from type 1 and 2 alcoholics. In particular, binding density was measured in brain regions that are associated with addiction and social processes; i.e., AINS, PINS, PCC, DLPFC, DMPFC, HIPP, PHG and DR, by using whole-hemisphere autoradiography. Results from other brain regions, from this same sample set, have already been published in several articles (Mantere et al. 2002, Storvik et al. 2006a, Storvik et al. 2006b, Storvik et al. 2007, Storvik et al. 2008).
MATERIALS AND METHODS

The methodology of this study has been described earlier (Tupala et al. 2001, Mantere et al. 2002, Storvik et al. 2009). Briefly, post-mortem brain left hemispheres (17 alcoholics and 8 controls) were obtained during clinical autopsy from the Department of Forensic Medicine, University of Oulu, Finland, and two of the non-alcoholic control brains were obtained from the Department of Forensic Medicine, University of Eastern Finland, Kuopio, Finland. The recovery procedure was essentially the same in both locations. This portion of the study was approved by the Ethics Committees of the University of Oulu (27.12.1997; latest amendment Dnro 125/2009) and the National Board of Medico-legal Affairs, Helsinki, Finland (Dnro 3020/322/96 and 3141/32/200/98). A post-mortem analysis for drugs, which included alcohol, and the normal necropsy protocol were performed. None of the hemispheres exhibited damage or gross neuroanatomical abnormalities, as judged from a series of Nissl stained sections. Medical records on the cause of death, previous diseases, and medical treatments of the controls and alcoholics were also collected.

Diagnostics

Diagnoses were made by two physicians independently of each other. Medical record data were available for all 27 subjects. Mental disorders were coded according to DSM-IV criteria (APA 1994), and alcoholic subjects were sub-classified as type 1 or 2, according to criteria established by Cloninger, which closely resembles the Babor and Early/Late onset typologies (Cloninger 1987, Leggio et al. 2009). The kappa coefficient of diagnostic agreement for the subjects was 0.9; i.e., one type 2 alcoholic was diagnosed as a type 1 alcoholic by the other physician. Otherwise, diagnoses were unanimous. The most important criteria for defining the two groups of alcoholic
Subjects were early onset (before the age of 25) of alcohol abuse and documented severe antisocial behaviour among the type 2 alcoholic subjects. Subjects having psychotic disorders or any neurological diseases (such as epilepsy), or those taking medication that could affect the CNS (such as neuroleptics or antidepressants, including the SSRIs) were excluded. A history of tobacco smoking and years of abuse, based only on medical records, were considered unreliable and were not included in the final criteria.

Study subjects

All 27 subjects were Finns. The study groups consisted of type 1 alcoholics (N=9, seven men and two women; age: mean=52.7 years, SD=12.4; post-mortem delay (PMI): mean=11.9 hours, SD=4.5); type 2 alcoholics (N=8, all men; age: mean=34.6 years, SD=12.2; PMI: mean=14.1 hours, SD=3.4); and non-alcoholic controls (N=10, eight men and two women; age: mean=53.5 years, SD=10.7; PMI: mean=14.8 hours, SD=9.2) (Table 1). All of the controls were free of a psychiatric diagnosis. Intervals between death and autopsy were not significantly different between the groups (P=0.62–0.98, Scheffe’s test for multiple comparisons, two-tailed). Six of the eight type 2 alcoholics had a criminal record or a history of violent offences (physical or sexual). Alcoholism in both type 1 and type 2 groups was severe, as judged by frequent admissions to emergency stations and doctors’ appointments due to alcohol-related problems. Two of the type 1 alcoholics had traces of diazepam in their blood samples. Three of the type 2 alcoholics had traces of benzodiazepines. One type 2 alcoholic tested positive for cannabinoids by radioimmuno assay, which was not confirmed by a more definitive test and could have been a false positive for ibuprofen. All subjects died of sudden causes.
Cryosectioning and autoradiography were performed at the School of Pharmacology and Toxicology, University of Eastern Finland, Kuopio, Finland, as previously described in (Mantere et al. 2002). Individual variations in brain size were also considered when selecting representative sections. Each cryosection was coded for a subsequent blind analysis of the data.

\[^3\text{H}\]Citalopram binding assay

The \[^3\text{H}\]citalopram binding assay has been described in detail in previously published articles (Mantere et al. 2002, Storvik et al. 2006a, Storvik et al. 2007). Briefly, the incubation concentration for \[^3\text{H}\]citalopram (specific activity= 82 Ci/mmol, NEN Life Science Products Inc., Boston, MA, USA) was 1.2nM in a phosphate buffer solution (137mM of sodium chloride, 2.7mM of potassium chloride, 1.8mM of potassium phosphate, and 10.1mM of hydrosodium phosphate; pH7.4). Pre-incubation (15 min) was made in the phosphate buffer at room temperature. The incubation (90 min at room temperature) was followed by three 10 minute washings in ice-cold phosphate buffer, followed by a brief dip in ice-cold distilled water. Non-specific binding was determined by incubating adjacent sections with 10\(\mu\)M of fluoxetine and 0.1% ascorbic acid. Sections were exposed to radiation-sensitive film (\[^3\text{H}\]-Hyperfilm, discontinued, Amersham, Buckinghamshire, UK) for 4 weeks with tritium calibration standards. The auto-radiograms were analysed by means of computerized densitometry and the resulting pixel values were mathematically transformed into physical tissue values (pmol/g). All analyses were made blind to the clinical classification of the samples. An adjacent section from the respective level was stained with cresyl violet (Nissl staining) to serve as an anatomical correlate to the autoradiography.
**Statistical analyses**

The variables were standardized (with a mean of zero and a standard deviation of one) to the same mean and distribution within brain area and across the study groups by standard deviation. In order to evaluate the overall difference in $[^3]$Hcitalopram binding between the study groups a mean of the z-scores was calculated and statistical significance between groups was evaluated by a permutation type ANOVA (Monte Carlo p-value). Effect size for this comparison was calculated using Cohen’s $f$. Cohen’s $f$ values over 0.4 were considered large. Confidence intervals for the effect sizes were obtained by bias-corrected bootstrapping (5000 replications). Correlation coefficients were calculated by the Pearson method. The $\alpha$ level was set at 0.05 for all tests. We used STATA (release 13.1, College Station TX) for all statistical analyses.
RESULTS

[^3]H]Citalopram binding was observed in all the measured brain regions (Figure 1) with highest binding in the DR. Statistically significant differences in the mean[^3]H]citalopram binding of all measured brain areas was observed between the study groups (Figure 2). Statistically significant differences were observed between the study groups in the PINS, PCC and PHG (Table 2).

No significant Pearson correlations were observed between age at the time of death and measured[^3]H]citalopram binding in any of the studied regions for any of the study groups. There were significant negative correlations between post-mortem interval (PMI) and[^3]H]citalopram binding in the PINS and AINS in type 2 alcoholics (R=-0.85 and -0.75, respectively). These correlations were not observed in type 1 alcoholics or controls. There were no significant correlations between PMI and[^3]H]citalopram binding in any of the other brain regions for any of the study groups. There was a negative correlation between blood alcohol concentration (BAC) and[^3]H]citalopram binding in the PINS of type 1 alcoholics (R=-0.69). However, this correlation was not observed in the other study groups. Moreover, there was a negative correlation between BAC and[^3]H]citalopram binding in the PCC of type 2 alcoholics (R=-0.77), which was not observed in the other study groups. No significant correlations between BAC and[^3]H]citalopram binding were observed in any other brain region for any of the study groups.
DISCUSSION

In the present study, we measured [3H]citalopram binding to SERT in eight brain regions of the post-mortem left hemispheres from Cloninger type 1 and 2 alcoholics and non-alcoholic controls. A statistically significant difference with a large effect size was observed in the mean [3H]citalopram binding between the study groups, with type 2 alcoholics having the lowest mean [3H]citalopram binding (Figure 2).

In the follow up analysis, low [3H]citalopram binding was observed in the PINS and PCC in both alcoholic groups when compared to non-alcoholic controls (Table 2), which is similar to previously published findings of low SERT densities in the ACC, caudate and amygdala of alcoholics (Mantere et al. 2002, Storvik et al. 2006a, Storvik et al. 2007). However, in the present study, only type 2 alcoholics had a low [3H]citalopram binding in the PHG (Table 2). Decreased [3H]citalopram binding in alcoholics could be an indication of decreased serotonergic activity in these brain areas, which may be associated with risk factors of developing alcoholism, for example severe childhood stress (Berglund et al. 2013), or with chronic and extensive alcohol consumption or a combination of these factors. However, it should also be noted that not all brain regions with serotonergic activity seem to be affected (table 2).

The PINS has a role in interoception and emotion recognition (Cauda et al. 2012, Paulus and Stewart 2014) while the PCC has been associated with social cognition (van Veen et al. 2009, Morey et al. 2012, Sperduti et al. 2012), and the left PCC in particular plays a critical role in the evaluation of negative social situations and emotions (Arsenault et al. 2013, Lemche et al. 2013). Both of these regions have been associated with cue reactivity (Garavan et al. 2000, Brewer and Garrison 2013, Dager et al. 2013, da Silva et al. 2013, Yokum and Stice 2013). Therefore, the low
[\(^3\)H]citalopram binding presently observed in the PINS and PCC of both alcoholic groups could be responsible for the dysfunctions in cognitive inhibition associated with alcohol cravings, in addition to the altered social cognition and emotional recognition commonly presented by alcoholics (Arsenault et al. 2013, Brewer et al. 2013, Lemche et al. 2013, Paulus and Stewart 2014). However, this putative serotonergic dysregulation of social cognitive processes seems to yield opposite reactions between harm avoiding type 1 alcoholics and impulsive type 2 alcoholics (Cloninger 1995).

HIPP and PHG are both associated with memory processes, but in the present study altered [\(^3\)H]citalopram binding was only observed in the PHG between the study groups (Table 2). The main function of PHG seems to be in context recognition, which is related to social perceptions (Aupperle et al. 2013, Rapp et al. 2013, Shi et al. 2013, Silk et al. 2013). Since no alteration was observed in the [\(^3\)H]citalopram binding in the hippocampus, the now observed low [\(^3\)H]citalopram binding in only the PHG of type 2 alcoholics could be associated with inadequate serotonergic modulation of social context recognition, and therefore explain some of the antisocial behaviours seen in these individuals (Cloninger 1987, Berglund et al. 2013).

As age is an integral part of the studied phenomenon (Cloninger 1987), and there were no large correlations between age and [\(^3\)H]citalopram binding, using age as a covariant would not have been a statistically valid procedure in the present study (Miller and Chapman 2001). Because there were no consistent correlations between the [\(^3\)H]citalopram binding and BAC or PMI in the present study, and opposite correlations have also been reported (Mantere et al. 2002), no confident conclusion can be made about the possible effect of BAC or PMI on [\(^3\)H]citalopram binding in post-mortem brain tissue.
In conclusion, even though the present results are preliminary, and from a relatively small diagnostic groups, they demonstrate lower $[^3]H$citalopram binding in the PINS and PCC of alcoholics when compared to non-alcoholic controls. This finding could explain the diminished serotonergic control over alcohol-cue reactivity, social cognition and emotion recognition. However, low $[^3]H$citalopram binding in the PHG was only observed in type 2 alcoholics, which could explain their diminished capacity for social context recognition. Further studies are needed to thoroughly understand the role of serotonergic alterations in the aetiology of alcoholism, and the possible role of serotonergic medications in the treatment of alcoholism.
ACKNOWLEDGEMENTS

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The present study would not have been possible without the highly appreciated initial contribution by Erkki Tupala, MD, PhD, deceased. We also wish to thank Pirkko Räsänen, MD, PhD; Terttu Särkioja, MD, PhD and Kari Karkola, MD, PhD for their help with the study; Ms. Aija Räsänen for dedicated secretarial services and James C. Callaway, PhD, for comments and editing the English language of this report.


Fig. 1. Representative picture of [$^3$H]citalopram binding in the post-mortem brain tissue of a type 2 alcoholic.

AINS, anterior insula; HIPP, hippocampus; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; DR, dorsal raphe nucleus; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; PINS, posterior insula.
Fig. 2. $[^3]$Hcitalopram bindings between the study groups.

Mean z-scores of $[^3]$Hcitalopram bindings in measured brain areas. Cohen’s $f=0.55$ (95%CI: 0.16-1.30).
Table 1. The study subjects: age at time of death, post-mortem interval (PMI), blood alcohol concentration (BAC) and cause of death.

<table>
<thead>
<tr>
<th>Group and subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>PMI (h)</th>
<th>BAC (%)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-alcoholic controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>55</td>
<td>5.5</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>45</td>
<td>9.5</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>77</td>
<td>7.5</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>57</td>
<td>11.0</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>50</td>
<td>18.5</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>60</td>
<td>12.0</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>49</td>
<td>33.0</td>
<td>0.4</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>53</td>
<td>11.0</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>53</td>
<td>11.0</td>
<td>0.0</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>36</td>
<td>11.0</td>
<td>0.0</td>
<td>Dissection of aorta</td>
</tr>
<tr>
<td><strong>Type 1 alcoholics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>39</td>
<td>12.5</td>
<td>0.0</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>48</td>
<td>4.5</td>
<td>0.1</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>45</td>
<td>12.0</td>
<td>1.5</td>
<td>Suicide by hanging</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>42</td>
<td>14.8</td>
<td>0.8</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>76</td>
<td>10.5</td>
<td>3.2</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>56</td>
<td>19.0</td>
<td>4.1</td>
<td>Ethanol intoxication</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>48</td>
<td>6.5</td>
<td>1.4</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>69</td>
<td>16.0</td>
<td>4.7</td>
<td>Ethanol intoxication</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>51</td>
<td>11.0</td>
<td>0.0</td>
<td>Right subdural hemorrhage</td>
</tr>
<tr>
<td><strong>Type 2 alcoholics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>49</td>
<td>12.0</td>
<td>1.7</td>
<td>Fibrotic degeneration of myocardium</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>37</td>
<td>9.5</td>
<td>3.0</td>
<td>Gunshot wound</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>47</td>
<td>15.5</td>
<td>3.0</td>
<td>Knife wound</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>20</td>
<td>14.5</td>
<td>1.3</td>
<td>Knife wound</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>46</td>
<td>18.0</td>
<td>0.0</td>
<td>Suicide by hanging</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>18</td>
<td>9.5</td>
<td>1.5</td>
<td>Heart rupture (car accident)</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>32</td>
<td>16.5</td>
<td>3.6</td>
<td>Suicide by hanging</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>28</td>
<td>17.5</td>
<td>0.0</td>
<td>Suicide by hanging</td>
</tr>
</tbody>
</table>
Table 2. [\(^3\)H]Citalopram binding in the measured brain areas.

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Mean binding (SD); pmol/g of tissue</th>
<th>P-value</th>
<th>Effect size (Cohen’s (\hat{f}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Type 1</td>
<td>Type 2</td>
</tr>
<tr>
<td>AINS</td>
<td>13.16 (±5.48)</td>
<td>11.57 (±3.96)</td>
<td>10.21 (±4.78)</td>
</tr>
<tr>
<td>PINS</td>
<td>19.08 (±3.51)</td>
<td>15.27 (±2.29)</td>
<td>13.68 (±4.85)</td>
</tr>
<tr>
<td>PCC</td>
<td>10.8 (±2.25)</td>
<td>7.64 (±2.86)</td>
<td>7.48 (±1.95)</td>
</tr>
<tr>
<td>DLPFC</td>
<td>8.5 (±3.3)</td>
<td>7.44 (±4.43)</td>
<td>4.58 (±1.76)</td>
</tr>
<tr>
<td>DMPFC</td>
<td>8.02 (±2.37)</td>
<td>7.88 (±3.97)</td>
<td>5.59 (±2.49)</td>
</tr>
<tr>
<td>PHG</td>
<td>13.46 (±3.48)</td>
<td>11.47 (±3.84)</td>
<td>7.81 (±3.67)</td>
</tr>
<tr>
<td>HIPP</td>
<td>7.72 (±3.55)</td>
<td>7.18 (±3.37)</td>
<td>7.18 (±3.49)</td>
</tr>
<tr>
<td>DR</td>
<td>59.05 (±13.71)</td>
<td>62.21 (±10.72)</td>
<td>59.8 (±15.43)</td>
</tr>
</tbody>
</table>

Mean binding and standard deviations of measured [\(^3\)H]citalopram binding in the post-mortem brains of Cloninger type 1 and 2 alcoholics and non-alcoholic controls. AINS, anterior insula; PINS, posterior insula; PCC, posterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; PHG, parahippocampal gyrus; HIPP, hippocampus; DR, dorsal raphe nucleus.