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NMDA receptors and BDNF are necessary for discrimination of overlapping spatial and non-spatial memories in perirhinal cortex and hippocampus

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Abstract

Successful memory involves not only remembering information over time but also keeping memories distinct and less confusable. Discrimination of overlapping representations has been investigated in the dentate gyrus (DG) of the hippocampus and largely in the perirhinal cortex (Prh). In particular, the DG was shown to be important for discrimination of overlapping spatial memories and Prh was shown to be important for discrimination of overlapping object memories. In the present study, we used both a DG-dependent and a Prh-dependent task and manipulated the load of similarity between either spatial or object stimuli during information encoding. We showed that N-methyl-D-aspartate-type glutamate receptors (NMDAR) and BDNF participate of the same cellular network during consolidation of both overlapping object and spatial memories in the Prh and DG, respectively. This argues in favor of conserved cellular mechanisms across regions despite anatomical differences.

Introduction

Memory is often thought of as the ability to remember information over time. However, the ability to separate memories of similar experiences into distinct representations that are resistant to confusion is crucial for accurate retrieval (Dickerson et al., 2010). This has been simulated in computational models by a process termed 'pattern separation' that transforms similar inputs into output representations that are less correlated with each other and there is electrophysiological evidence of such transformation in the DG (Leutgeb et al., 2007) and Prh (Ahn et al., 2017). The study of this process may be relevant to understanding memory loss in aging and pathological conditions. For example, it has been reported that patients with schizophrenia or Alzheimer's disease show memory deficits related to the inability to keep memories distinct (Ally et al., 2013; Das et al., 2014; Llorens-Martin et al., 2014). The DG of the hippocampus (HC) was proposed as crucial for this cognitive function (Ranganath, 2010), and adult neurogenesis in the DG was shown to be necessary for normal behavioral pattern separation (Bekinschtein et al., 2014b; Clelland et al., 2009). However, previous

work has pointed at the Prh as a structure also important for separation of overlapping experiences involving highly similar objects (Bartko et al., 2007a; b; Miranda et al., 2017).

The dominant experimental models for cellular mechanisms underlying learning and memory are long-term potentiation (LTP) and long-term depression (LTD). While the intracellular processes involved in LTP and LTD have been mainly studied in the hippocampus (HP) (Takeuchi et al., 2014), several of the synaptic plasticity mechanisms that operate in the HP seem to also play a part in PRh, and in fact LTD is candidate processes for the effective storage of recognition memories in the PRh (Griffiths et al., 2008). Although there are mechanistically distinct forms of LTP and LTD, it is largely accepted that NMDAR are central to at least some forms of LTP and LTD (Collingridge et al., 1983; Dudek et al., 1992; Malenka et al., 1992). However, DG NMDAR are not always essential for spatial learning and memory, which suggests they may have a subtler role (Bannerman et al., 1995;; Saucier et al., 1995). For example, selective knockout of the NR1 subunit of the NMDAR in the DG in mice impaired the ability to distinguish between contexts, but interestingly did not impair memory for contextual fear (McHugh et al., 2007).

Brain-derived neurotrophic factor (BDNF) is important for excitatory synaptic transmission and plasticity, and plays a crucial role in learning and memory (Bekinschtein et al., 2014a). We have shown that BDNF mediates plasticity mechanisms required for consolidation of similar and not dissimilar memories in the PRh and DG (Bekinschtein et al., 2013; Miranda et al., 2017). Previous studies showed that BDNF promotes phosphorylation of NMDAR, leading to an enhancement of NMDAR activity (Levine et al., 1998; Lin et al., 1998; Mizuno et al., 2003; Suen et al., 1997). This process could be a potential effector mechanism for the plastic actions of BDNF on consolidation of overlapping memories.

In this work, we used modified versions of the spontaneous recognition and object location tasks (Bekinschtein et al., 2013; Miranda et al., 2017) and pharmacological methods to interfere or potentiate the possible molecular mechanisms involved in separating overlapping memories. We show that BDNF is involved in the acquisition/consolidation of both spatial and non-spatial overlapping memories. In addition, we found evidence that the BDNF and NMDAR-dependent molecular pathways interact during consolidation of overlapping spatial and object memories in the DG and Prh.

Experimental procedures

Subjects

The subjects were 52 Long Evans rats from our breeding colony, weighing approximately 250-300 g at the start of testing. The rats were housed on a reversed 12 h light/12 h dark cycle (lights on 19:00-07:00), in groups of two or four. All behavioral testing was conducted during the dark phase of the cycle. Rats were food restricted to 85-90% of their free feeding weight, except during recovery from surgery, where food was available *ad libitum*. Water remained available *ad libitum* throughout the experiments. All experimentation was conducted in accordance with the National Animal Care and Use Committee of Favaloro University (CICUAL) and in strict compliance with the guidelines of the University of Cambridge and United Kingdom Animals (Scientific Procedures) Act 1986 and the Amendment Regulations 2012.

Surgery and cannulation

Rats were implanted bilaterally in Prh or DG with 22-gauge indwelling guide cannulas. Subjects were anaesthetised with ketamine (Holliday, 74 mg kg⁻¹, i.p.) and xylazine (Konig, 7.4 mg kg⁻¹, i.p.) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set at -3.2 mm. Guide cannulas were implanted according to the following coordinates (measured relative to the skull at bregma (Paxinos and Watson, 1998)): for Prh cannulation anteroposterior -5.5 mm, lateral ±6.6 mm, dorsoventral -7.1 mm; for DG cannulation anteroposterior -3.9 mm, lateral ± 1.9 mm, dorsoventral -3.0 mm. Obturators with an outer diameter of 0.36 mm were inserted into the guides. At the completion of each surgery, an antibiotic was applied for three days (Enrofloxacin; 0.27 mg kg⁻¹, Vetanco, Arg). Animals were given at least 7 days to recover prior to drug infusions and behavioral testing.

Infusion procedure

Depending on the experiment, rats received bilateral infusions of either oligonucleotides (ODNs, 4 nmolµl⁻¹/0.5 µl side; Genbiotech), recombinant human BDNF (rhBDNF; 0.5 µg/0.5 µl side; Bioscience, Cambridge, UK), competitive NMDA antagonist AP5 (D(-)-2-amino-5-phosphonopentanoic acid, 2 µg/µl and 0.5 µl side) or saline (Veh) at different times during the behavioral task. ODNs were dissolved in sterile saline to a concentration of 4 nmolµl⁻¹. All ODNs were phosphorothioated on the three terminal bases of both 5' and 3' ends for increased stability and less toxicity of the ODN. Control missense oligonucleotides (MSO) included the same 18 nucleotides as the antisense oligonucleotides (ASO) but in a scrambled order gene. BDNF ASO, 5'-TCTTCCCCTTTTAATGGT-3'; BDNF MSO, 5'-ATACTTTCTGTTCTTGCC-3'. Due to their large size and slower mechanism of action, unlike AP5, oligonucleotides were injected 2 h before the beginning of the sample phase to ensure they were sufficiently taken by the cells and present during the behavioral experience.

Apparatus

For details of the apparatus and the objects see (Bekinschtein et al., 2013; Miranda et al., 2017).

Behavioral procedures

The SOR and SLR tasks were run exactly as previously described (Bekinschtein et al., 2013; Miranda et al., 2017). For all the experiments, the results were expressed as a discrimination ratio that was calculated as the time exploring the novel object (spontaneous object recognition, SOR) or the object in the novel location (spontaneous location recognition, SLR) minus the time exploring the familiar object (SOR) or the object in the familiar location (SLR) over total exploration time ($(t_{\text{novel}} - t_{\text{familiar}}) / t_{\text{total}}$). Scoring was done blinded to the treatment. Discrimination ratios were compared within subject using a paired *t* test. For experiments shown in Figure 3F and 2F, rats were tested three times. For each trial, a different set of objects was used and at least two days were given between repeated trials to allow washout of the drug. Rats were pseudorandomly assigned to one of the following groups in the first trial: one third of the animals received AP5 injection combined with BDNF injection, another

third received Vehicle injection combined with BDNF, and the final third received Vehicle injection combined with Vehicle injection. In the second and third trials the rats were injected with either BDNF and Vehicle, BDNF and AP5 or Vehicle and Vehicle depending on the previous treatment. For the “molecular disconnection” experiment, when BDNF-ASO and AP5 were injected into the region (either DG or PRh) of one hemisphere or different hemispheres, BDNF-MSO and Veh were injected into the other hemisphere. For the behavioral experiments depicted in Figure 1B and 2B, rats were tested three times with different object combinations and discrimination ratios were compared within subject, using a Repeated Measures One way ANOVA followed by Tukey post-hoc comparisons. In all experiments, the order of the treatments was counterbalanced.

Histology

Upon completion of behavioral testing, the rats were anaesthetized by IP injection with 2 ml of Euthatal (Rhône Merieux) and perfused transcardially with phosphate buffered saline (PBS), followed by 10% neutral buffered formalin. The brains were postfixed in formalin for 24 hours before being immersed in 20% sucrose solution for 48 h. Forty- μ m sections were cut on a freezing microtome. Every fifth section was mounted on a gelatin-coated glass slide and stained with safranin.

Results

To explore the interaction between NMDAr and BDNF on overlapping spatial memories, we used a modified version of the spontaneous location recognition task (SLR) (Bekinschtein et al., 2013). In our modified version of the SLR, we manipulated the similarity between object locations by changing the distance between objects during encoding (see Methods). Previous work using this task has shown that blockade of BDNF in the DG affected memory on the small separation (similar) but not the large separation (dissimilar) condition, establishing a separation-dependent effect (Bekinschtein et al., 2013; 2014b).

“Molecular disconnection” suggests NMDAr and BDNF are part of the same cellular network required for discrimination of overlapping spatial memories in DG

We asked whether BDNF was interacting with NMDAr to exert its effects on spatial memories. To tackle this question, we carried out a “molecular disconnection” experiment (Miranda et al, 2017) that applies the same rationale of a typical disconnection experiment between structures (e.g., (Belin et al., 2008)). For example, if we think of two molecular or gene expression pathways within a given structure, blocking both of them in that region of one hemisphere may not have any effect because the processes in the other hemisphere remain intact; in contrast, blockade of one molecule in one hemisphere and the second molecule in the other hemisphere would produce a deficit in the case that both molecular pathways are directly or indirectly connected. Thus, in the present study we blocked BDNF expression -using a BDNF-ASO- and NMDAr activity in the DG- using AP5- in either the same hemisphere or opposite hemispheres (Fig.2A). MSO and Veh in the case of AP5 were used in the opposite hemisphere for each injection as a control. BDNF-ASO was injected 2h before the sample phase and AP5 15 min before to sample phase (s-SLR, see Fig.1C). The difference in the infusion times is related to the fact that oligonucleotides are large molecules and it takes more time for them to be taken by the cells. The results showed that when the BDNF-ASO and AP5 were injected into the same hemisphere, there were no effects in the s-

SLR condition, which was evaluated at 24h. However, when the injections were into different hemispheres, performance was significantly impaired (paired t test, $p = 0.032$, $t = 2.59$) (Fig.2C). As expected, rats spent equal total amounts of time exploring during the sample phases, regardless of the pre-sample treatment ($p = 0.093$) (Fig.2B). These results suggest that BDNF and NMDAR are interacting directly or indirectly during the acquisition/consolidation of overlapping spatial memories in the DG. In addition, we found that bilateral infusion of AP5 into the DG 15 min before the sample phase did not affect short-term memory evaluated 1,5 h post-sample (discrimination indexes: 0.18 ± 0.05 (Veh) vs 0.21 ± 0.08 (AP5), mean \pm SEM, $p = 0.78$, paired t test, $n = 8$). This result suggests that BDNF and NMDAR interaction likely occurs during consolidation of long-term memory.

NMDAR activation and BDNF are necessary to enhance discrimination of overlapping memories in the DG

Previous work showed that injection of recombinant BDNF (rBDNF) in the DG is capable of improving the consolidation of overlapping spatial memories (Bekinschtein et al., 2013). We asked whether NMDAR could be required for the enhancing effect of rBDNF. We reasoned that if BDNF and NMDAR activation are both required for memory enhancement, then inhibition of NMDAR activity would prevent it. To test this, we used the xs-SLR condition of the task, where positions of the objects during the sample phase are closer and thus the discrimination is more difficult (Fig.1C), and combined 15 min pre-sample AP5 with post-sample rBDNF infusions into the DG. After 24 h, vehicle-injected rats could not recognize the new location as novel (Fig.2D). As predicted, rBDNF enhanced performance significantly compared with vehicle-infused animals, but this effect was abolished by AP5 (RM-ANOVA, $p < 0.001$, $F = 35.319$) (Fig.2F). Analysis confirmed that rats spent equal total amounts of time exploring during the sample phases, regardless of the pre-sample treatment ($p = 0.60$) (Fig.2E). The results of this experiment demonstrate that pre-sample infusion of AP5 into the DG blocked the post-sample effect of BDNF, which suggests that NMDAR activation is part of the mechanism involved in BDNF-dependent consolidation of overlapping spatial memories.

BDNF and NMDAR are part of the same cellular network required for discrimination of overlapping object memories in the Prh

To investigate the interaction between BDNF and NMDAR during separation of non-spatial experiences, we used the SOR task that has analogous similar (s-SOR) and dissimilar (d-SOR) versions, allowing for the similarity of the objects to be varied. For SOR, similarity is determined by the number of features that a pair of objects shares (Miranda et al., 2017). This task allows for a comparison between the molecular mechanisms involved in discrimination between the Prh and the DG. Analogous to the experiment described above using the SLR task, we carried out a “molecular disconnection” experiment in the Prh using the SOR task. We injected AP5 and BDNF-ASO into the Prh of the same hemisphere or the Prh of different hemispheres before the sample phase in the s-SOR version of the task (Fig.3A). Infusion of BDNF-ASO and AP5 into the same hemisphere had no effect on memory, but rats injected into the Prh in different hemispheres were impaired in their ability to discriminate the novel object in the s-SOR (paired t test, $p = 0.0006$, $t = 4.942$) (Fig.3C). Total amount of time spent exploring during the sample phase did not differ between conditions ($p = 0.286$) (Fig.3B). This indicates that the interaction of the BDNF- and NMDAR-

dependent pathways is necessary for the separation of overlapping object memories in the Prh (Fig.3C). In addition, we found that bilateral infusion of AP5 into the Prh 15 min before the sample phase did not affect short-term memory evaluated 1,5 h post-sample (discrimination indexes: 0.19 ± 0.06 (Veh) vs 0.19 ± 0.05 (AP5), mean \pm SEM, $p=0,97$, paired t test, $n=7$). This result suggests that BDNF and NMDAr interaction likely occurs during consolidation of long-term memory.

NMDAr activation and BDNF are necessary to enhance discrimination of overlapping memories in the Prh

Similar to the DG, injection of rBDNF in the Prh enhances the consolidation of overlapping object memories (Miranda et al., 2017), thus we explored whether NMDAr are required for rBDNF discrimination enhancement. To test this, we used the more challenging xs-SOR condition, which reduces performance to chance levels (Miranda et al., 2017) and injected AP5 15 min before and rBDNF immediately after the sample phase of the xs-SLR in the Prh (Fig.3D). Vehicle-injected animals were not able to identify the novel object at 24h, whereas rBDNF-injected animals showed a preference for the novel object. However, when rBDNF was combined with AP5 injection, performance remained at chance levels, suggesting that the AP5 prevented the enhancement associated with rBDNF (RM-ANOVA, $p = 0.0058$, $F = 9.288$, Fig.3D). Rats spent equal total amounts of time exploring during the sample phases, regardless of the pre-sample treatment ($p = 0.25$) (Fig.3E). These results point suggest that NMDAr are acting in conjunction with BDNF in the consolidation of overlapping memories in a domain-independent manner in both the DG and Prh.

Discussion

In this work, we explored the critical molecular events underlying the mnemonic process of disambiguation of overlapping memories and identified NMDAr as a critical players for BDNF action in memory consolidation in both the object and the spatial domains. This suggests that cellular mechanisms driving consolidation of overlapping memories appear to be similar across different brain regions and for different kinds of stimuli.

We previously showed that BDNF in both the DG and the Prh is critically involved in the molecular mechanisms underlying storage of overlapping memories (Bekinschtein et al., 2013; Miranda et al., 2017). Specifically, the expression of BDNF in the DG is spontaneously increased after rats are exposed to similar, but not dissimilar spatial locations, and both object and spatial representations go through a time-restricted consolidation phase in the Prh and DG respectively (Bekinschtein et al., 2013; Miranda et al., 2017). Moreover, disrupting BDNF affected performance only in the similar version of the tasks and rBDNF in the DG and Prh improves performance in an extra-similar version of both the SLR and SOR tasks respectively. These findings suggest that rats engage a BDNF-associated process to separate overlapping memories when faced with ambiguous information, specifically in the structure where this information is processed.

Here, we went a step further and demonstrated that BDNF is interacting with NMDAr-dependent mechanism to mediate the consolidation of overlapping memories in both the Prh and DG. While unilateral or bilateral blockade of BDNF or NMDAr alone would not have given any information regarding a putative functional interaction between these pathways, comparison of combined unilateral blockade of BDNF and NMDAr in the opposite

hemispheres in respect to the same hemisphere showed that both BDNF and NMDAR-dependent pathways need to be active within the same region of the same hemisphere for successful processing, which suggests that NMDAR interact directly or indirectly with BDNF during the disambiguation of both spatial and object memories in the DG and the Prh respectively. Importantly, rBDNF enhances mnemonic discrimination and NMDAR activation is required for the enhancement. These findings are consistent with evidence demonstrating that NMDAR are required for spatial pattern separation and discrimination learning under certain circumstances (McHugh et al., 2007 (Brigman et al., 2008) and with a role in the formation of object recognition memory and spatial memory (Barker et al., 2006; Shimizu et al., 2000). These results are consistent with a wider literature suggesting that NMDAR are candidate mediators for BDNF-induced plastic changes (Levine et al., 1998; Lin et al., 1998; Mizuno et al., 2003; Rostas et al., 1996; Suen et al., 1997).

Further work is needed to elucidate the exact mechanism by which BDNF interacts with the NMDAR cellular pathway in the DG and Prh. Previous work has shown that BDNF can modulate glutamatergic pathways (Drake et al., 1999). BDNF rapidly enhances synaptic transmission postsynaptically by selectively modulating the probability of opening of NMDAR through phosphorylation of the modulatory NR2B NMDAR subunit (Crozier et al., 1999; Levine et al., 1998; Lin et al., 1998; Suen et al., 1997). However, there is evidence that BDNF-dependent long-term potentiation does not require NMDAR activation (Messouadi et al., 2002). On the presynaptic side, BDNF enhances glutamate release in synaptosomes (Pascual et al., 2001; Sala et al., 1998) and the frequency of miniature excitatory postsynaptic currents (mEPSCs) in brain slices and culture preparations, and this effect is also NMDAR-dependent (Madara et al., 2008). In addition, BDNF increases the translation of NMDAR mRNA (Caldeira et al., 2007) which could be dependent on the RNA-binding protein heterogeneous nuclear ribonucleoprotein K (hnRNP K), at least in cultured synaptoneuroosomes (Leal et al., 2017). Through its actions on NMDAR function, BDNF might modulate LTP by lowering the threshold of LTP induction through the enhancement of Ca²⁺ influx into dendritic spines (Kovalchuk et al., 2002). In fact, BDNF-induced plasticity and memory have been linked to NMDAR activation in the HC (Mizuno et al., 2003; Nakai et al., 2014; Suen et al., 1997), but there was no previous evidence for a similar NMDAR-BDNF interaction in the Prh *in vivo* or *in vitro* or in the HC during discrimination of overlapping memories. Our results suggest that NMDAR could be effectors of BDNF during the consolidation of overlapping memories. However due to the order of the infusions, AP5 was given prior to the sample phase, we cannot speculate on a particular order of interaction. One hypothesis for how BDNF and NMDAs might interact is that the key molecule linking BDNF and NMDAR is the tyrosine kinase Fyn. Fyn binds to NMDAR and TrkB (Takagi et al., 1999), mediates NR2B phosphorylation at Tyr-1472 (Nakazawa et al., 2001) and is necessary for hippocampal LTP and spatial learning (Grant et al., 1992). BDNF stimulates TrkB receptors, resulting in its association with Fyn, and the activated Fyn binds to NR2A and NR2B via SH2 domains (Iwasaki et al., 1998). Mizuno et al. (2003) showed that TrkB-Fyn-NR2B protein interaction increases during behavioral tests for spatial learning. Alternatively, other Src tyrosine kinases could be involved in this process. In this regard, Nakai et al. (2014) showed that BDNF-triggered PI3-K/Akt activation through TrkB can lead to the phosphorylation of Girdin S1416. Girdin S1416 then interacts with Src and NR2B to increase Src-mediated Y1472 phosphorylation of NR2B. This ultimately leads to larger LTP responses through increased head volume and PSDs with an increased NMDA/AMPA ratio of thin spines in the HC (Itoh et al., 2016). In sum, this study provides new evidence of the

molecular pathways involved in separate storage of overlapping memories in the Prh and the DG. Our results point toward an evolutionary convergence of the cellular mechanisms involved in plasticity required for this process across different regions of the brain with distinct anatomical structures.

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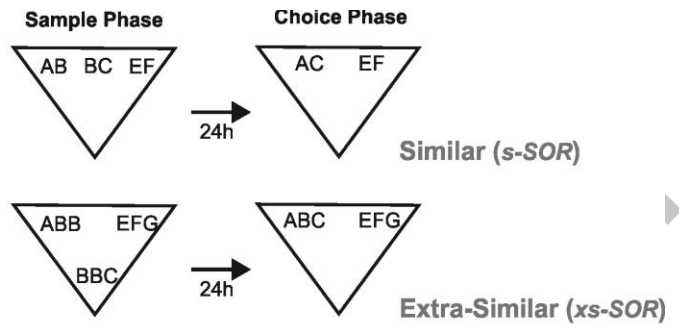
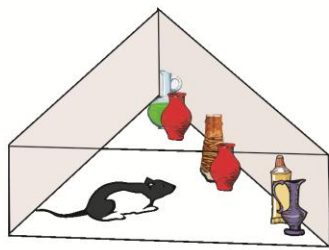
Figure Legends

Fig. 1. Description of the spontaneous object recognition task and spontaneous object location task. (A) (Left) Cartoon depicting the apparatus and the spontaneous object recognition task (SOR). (Right) Schematic illustration of the similar and extra-similar configurations of the SOR task. (B) Representative objects for the similar and extra-similar versions of the SOR task. (C) (Left) Cartoon depicting the apparatus and the spontaneous location recognition task (SLR). (Right) Schematic illustration of the two configurations of the SLR task.

Fig. 2. BDNF and NMDA are part of the same cellular network required for discrimination of overlapping object memories in the DG. (A) Schematic illustration of the configuration of the s-SLR task depicting the time point at which BDNF ASO and AP5 were infused in the DG. (B) Percentage of time spent exploring each of the objects in the sample phase in the s-SLR after BDNF ASO and AP5 were infused in the DG of the same (light color) or different hemispheres (dark color). There were no significant differences in the time spent exploring the objects between the same and different hemisphere groups ($p=0.16$), nor in the time spent exploring each of the object positions ($p=0.840$). (C) Effect of co-infusion of BDNF ASO and AP5 into the DG of the same or different hemispheres in the s-SLR task. Paired t test ($t= 3.116$) $p= 0.0124$; $n= 10$. (D) Schematic illustration of the configuration of the xs-SLR task depicting the time point at which BDNF ASO and AP5 were infused. (E) Percentage of time spent exploring each of the objects in the sample phase in the xs-SLR after Veh (light color) or AP5 infusion (dark color). There was no significant difference in the amount of time spent exploring each of the locations during the sample phase, and no effect of treatment ($p = 0.40$) or location ($p = 0.06$). (F) Effect of the co-infusion of BDNF and AP5 into DG in the xs-SLR task. RM-One Way ANOVA ($F=35.32$) $p<0.0001$; $n=7$. (G) Coronal section showing the track of the cannula and indicating representative infusion sites in the DG. Data are expressed as the mean \pm SEM; * $p<0.05$, *** $p< 0.001$. A1, A2 and A3 represent the positions of three copies of the same object.

Fig. 3. BDNF and NMDA α are part of the same cellular network required for discrimination of overlapping object memories in the Prh. (A) Schematic illustration of the configuration of the s-SOR task depicting the time point at which BDNF ASO and AP5 were infused in the Prh. (B) Percentage of time spent exploring each of the objects in the sample phase in the s-SOR after BDNF ASO and AP5 were infused in the PRH of the same (light color) or different hemispheres (dark color). There was no effect of the object ($p=0.425$) nor the group ($p=0.124$) in the time spent exploring each object. (C) Effect of the infusion of BDNF ASO and AP5 into the PRH of the same or different hemispheres in the s-SOR task. Paired t test, $t=4.942$, $p=0.0006$; $n=11$. (D) Schematic illustration of the configuration of the xs-SOR task depicting the time point at which BDNF ASO and AP5 were infused. (E) Percentage of time spent exploring each of the objects in the sample phase in the xs-SOR after Veh (light color) or AP5 infusion (dark color). There were no significant differences in the exploration time during the sample phase between groups ($p=0.09$) or between objects ($p=0.512$). (F) Effect of the co-infusion of BDNF α and AP5 into PRH in the xs-SOR task. RM-One Way ANOVA ($F=1.765$) $p=0.0058$; $n=10$. (G) Coronal section showing the track of the cannula and indicating representative infusion sites in the DG. Data are expressed as the mean \pm SEM; * $p<0.05$, ** $p<0.01$, *** $p<0.001$. AB, BC, EF, AC, ABB, BBC, EFG and ABC represent the different object compositions used for the task.

A



B

Similar



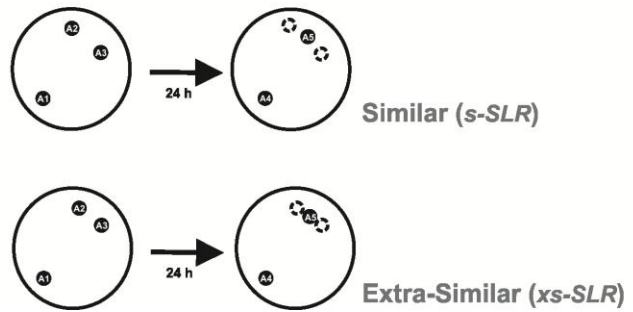
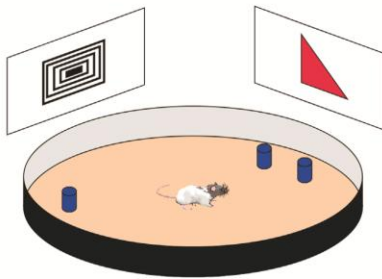
AB BC EF

Extra-similar

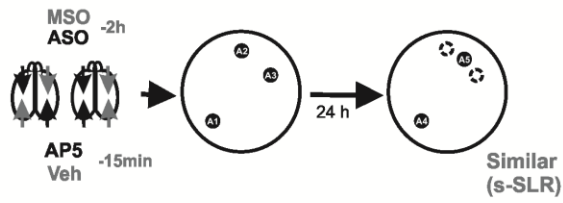
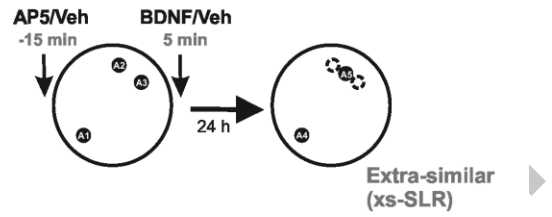
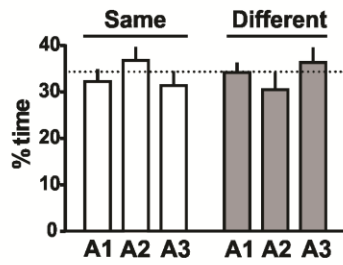
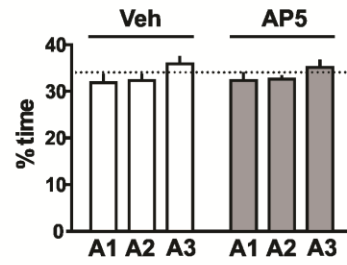
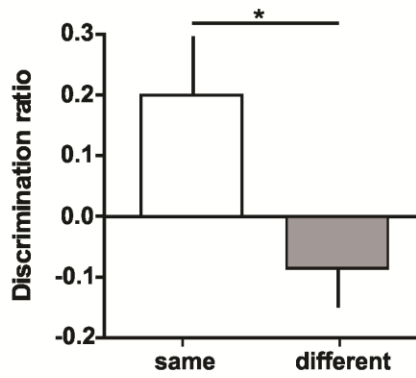
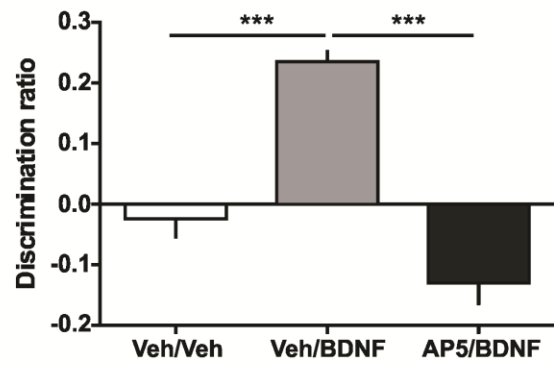
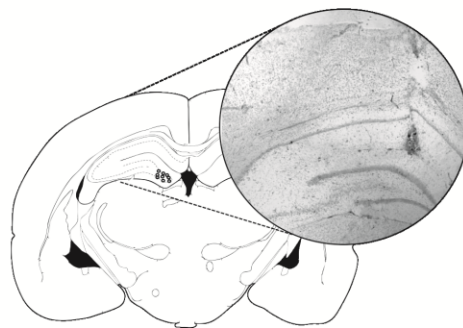


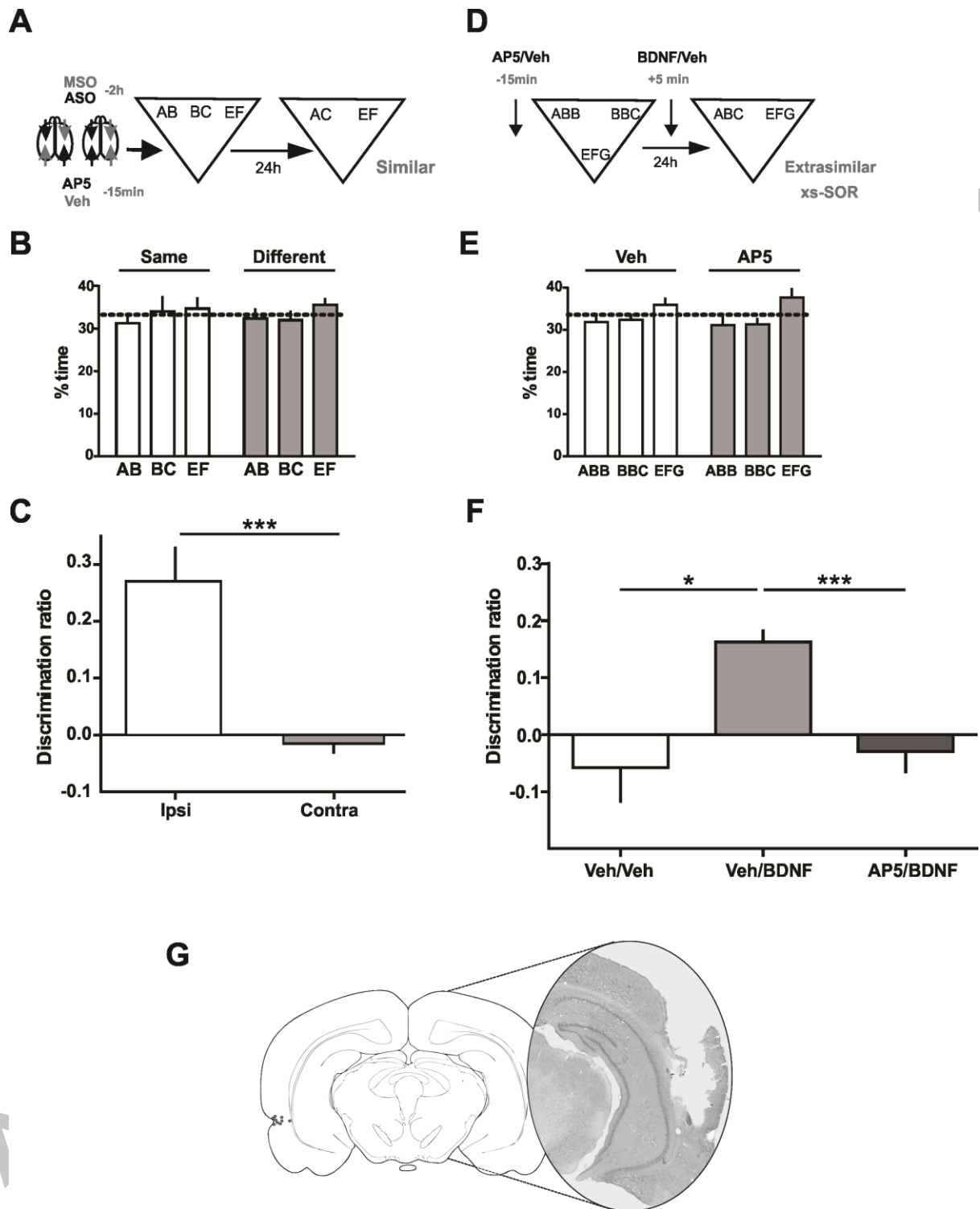
ABB BBC EFG

C



ACCEPTED

A**D****B****E****C****F****G**



Highlights

- Blockade of NMDAr activity and BDNF expression in the dentate gyrus of different hemispheres, but not of the same hemispheres impaired discrimination of spatial overlapping memories
- Blockade of NMDAr activity and BDNF expression in the perirhinal cortex of different hemispheres, but not of the same hemispheres impaired discrimination of object overlapping memories
- Blockade of NMDAr activity in the dentate gyrus prevented the enhancement of discrimination of spatial overlapping memories produced by recombinant BDNF infusion
- Blockade of NMDAr activity in the perirhinal cortex prevented the enhancement of discrimination of object overlapping memories produced by recombinant BDNF infusion
- NMDAr and BDNF cellular pathways interact during discrimination of overlapping memories in the dentate gyrus and the perirhinal cortex