1 The GluA1 cytoplasmic tail regulates intracellular AMPA receptor trafficking and synaptic

transmission onto dentate gyrus GABAergic interneurons, gating response to novelty

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### 12 **Abstract**

14 10 The GluA1 subunit, encoded by the putative schizophrenia-associated gene GRIA1, is required 15 for activity-regulated AMPA receptor (AMPAR) trafficking, and plays a key role in cognitive and 15 for activity-regulated AMPA receptor (AMPAR) trafficking, and plays a key role in cognitive and<br>16 affective function. The cytoplasmic, carboxy-terminal domain (CTD) is the most divergent region acros<br>17 AMPAR subunits. 16 affective function. The cytoplasmic, carboxy-terminal domain (CTD) is the most divergent regio<br>17 AMPAR subunits. The GluA1 CTD has received considerable attention for its role during long-ter<br>18 potentiation (LTP) at C 17 AMPAR subunits. The GluA1 CTD has received considerable attention for its role during long-term<br>18 potentiation (LTP) at CA1 pyramidal neuron synapses. However, its function at other synapses and,<br>19 more broadly, its c 18 potentiation (LTP) at CA1 pyramidal neuron synapses. However, its function at other synapses and<br>19 more broadly, its contribution to different GluA1 dependent processes, is poorly understood. Here<br>18 used mice with a c 19 more broadly, its contribution to different GluA1-dependent processes, is poorly understood. Here,<br>18 weed mice with a constitutive truncation of the GluA1 CTD to dissect its role regulating AMPAR<br>18 localization and fu 19 more broadly, its contribution of the GluA1 CTD to dissect its role regulating AMPAR<br>19 more with a constitutive truncation of the GluA1 CTD to dissect its role regulating AMPAR<br>19 More in the directed AMPAR subunit le 21 localization and function as well as its contribution to cognitive and affective processes. We fou<br>22 GluA1 CTD truncation affected AMPAR subunit levels and intracellular trafficking.  $\Delta$ CTD GluA1<br>23 exhibited no memor 22 GluA1 CTD truncation affected AMPAR subunit levels and intracellular trafficking.  $\Delta$ CTD GluA1 mice<br>23 exhibited no memory deficits, but presented exacerbated novelty-induced hyperlocomotion and<br>24 dentate gyrus granul 22 External Communication and Communication affection and dentate gyrus granule cell (DG GC) hyperactivity, among other behavioral alterations. Mechanisticall<br>25 Glue found that AMPAR EPSCs onto DG GABAergic interneurons w 24 dentate gyrus granule cell (DG GC) hyperactivity, among other behavioral alterations. Mechanisti<br>25 we found that AMPAR EPSCs onto DG GABAergic interneurons were significantly reduced, presure<br>26 underlying, at least in 25 we found that AMPAR EPSCs onto DG GABAergic interneurons were significantly reduced, presumably<br>26 underlying, at least in part, the observed changes in neuronal activity and behavior. In summary, this<br>27 study dissocia 26 underlying, at least in part, the observed changes in neuronal activity and behavior. In summary, this study dissociates CTD-dependent from CTD-independent GluA1 functions, unveiling the GluA1 CTD as a crucial hub regul underlying, at least in part, the observed changes in neuronal activity and behavior. In summary, this<br>27 study dissociates CTD-dependent from CTD-independent GluA1 functions, unveiling the GluA1 CTD as<br>28 a crucial hub re 28 a crucial hub regulating AMPAR function in a cell type-specific manner.<br>29 **Keywords:** AMPA receptor, GluA1, C-tail, Carboxy-terminal domain, schizophrenia, dentate gyrus,<br>31 novelty response, LTP, intracellular traffic 28 a crucial hub regulating Ammerical Hub regulation is competended.<br>28 **Keywords:** AMPA receptor, GluA1, C-tail, Carboxy-terminal domain, scl<br>31 novelty response, LTP, intracellular trafficking, PV+ interneuron.<br>32 29

31 Neywords: AMPA receptor, GluA1, C-tail, Carboxy-terminal domain, schizophrenia, dentate gyrus,<br>31 novelty response, LTP, intracellular trafficking, PV+ interneuron.<br>32

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33 Introduction 35 synapses throughout the CNS. Additionally, specific and sustained increases in the postsynaptic<br>36 AMPAR complement underlie long-term potentiation (LTP) (Kauer, Malenka et al. 1988, Muller, Joly<br>37 al. 1988), which pla 36 AMPAR complement underlie long-term potentiation (LTP) (Kauer, Malenka et al. 1988, Muller, al. 1988), which plays a crucial role in forms of learning and memory (Martin, Grimwood et al. 20<br>33 Nicoll 2017, Gall, Le et a 37 al. 1988), which plays a crucial role in forms of learning and memory (Martin, Grimwood et al. 2000,<br>38 Nicoll 2017, Gall, Le et al. 2024). AMPARs assemble into heterotetramers of pore-forming subunits<br>39 (GluA1-4), dec 38 Nicoll 2017, Gall, Le et al. 2024). AMPARs assemble into heterotetramers of pore-forming subunits<br>39 (GluA1-4), decorated by auxiliary subunits. Subunit composition imparts AMPARs' biophysical<br>30 properties and traffick 39 (GluA1-4), decorated by auxiliary subunits. Subunit composition imparts AMPARs' biophysical<br>30 properties and trafficking behavior (Malinow and Malenka 2002, Collingridge, Isaac et al. 2004, Dier<br>31 and Huganir 2018, Ha 39 (Gluban, Matematical), demain, 2010 (Malinow and Malenka 2002, Collingridge, Isaac et al. 2004,<br>39 and Huganir 2018, Hansen, Wollmuth et al. 2021, Bessa-Neto and Choquet 2023). At hippocam<br>39 synapses, GluA1-containing 10 properties and districting behavior (Malinow and Malenka 2002) collingings), isaac et al. 2004) of entiry<br>11 and Huganir 2018, Hansen, Wollmuth et al. 2021, Bessa-Neto and Choquet 2023). At hippocampal CA1<br>12 synapses, 11 and Huganir 2021, Hansen, Hansen Particular Particule and The Joseph Endphason.<br>141 and Huganism (Zamanillo, Sprengel et al. 1999, Hayashi, Shi et al. 2000, Shi, Hayashi et al. 2001). However, AMPAR<br>14 subunit compositi 43 (Zamanillo, Sprengel et al. 1999, Hayashi, Shi et al. 2000, Shi, Hayashi et al. 2001). However, AMPA<br>44 subunit composition varies dramatically among cell types and brain regions (Schwenk, Baehrens et<br>45 2014), and our 44 subunit composition varies dramatically among cell types and brain regions (Schwenk, Baehrens et al.<br>2014), and our understanding of the mechanisms underlying AMPAR trafficking and function at other<br>46 synapses, particu 44 subunit composition varies dramatically among cell types and brain regions (Schwenk, Baehrens et al.

1914), and our understanding or included<br>146 synapses, particularly at synapses onto inhibitory neurons, is limited.<br>147 Structurally, AMPAR subunits contain an amino-terminal domain (ATD, a.k.a. NTD), a ligand-<br>148 bindin 47 Structurally, AMPAR subunits contain an amino-terminal don<br>48 binding domain (LBD), a transmembrane domain which forms the po<br>49 terminal domain (CTD). Of all these regions, the CTD is the most sequ 1999 binding domain (LBD), a transmembrane domain which forms the pore channel, and a carboxylterminal domain (CTD). Of all these regions, the CTD is the most sequence-diverse, and has therefore<br>1990 terminal domain (CTD). 19 binding domain (CTD), Of all these regions, the CTD is the most sequence-diverse, and has ther<br>19 binding domain (CTD), Of all these regions, the CTD is the most sequence-diverse, and has ther<br>19 die - (Malinow and Male 19 terminal domain (CTD). Of all these regions, the CTD is an amount specific AMPAR trafficking rules<br>19 terminal domain (Malinow and Malenka 2002, Diering and Huganir 2018, Diaz-Alonso and Nicoll 2021, Bessa-Neto and<br>19 C 51 (Malinow and Malenka 2002, Diering and Huganir 2018, Diaz-Alonso and Nicoll 2021, Bessa-Neto<br>52 Choquet 2023, Stockwell, Watson et al. 2024). The GluA2 CTD plays an important role in synaptic<br>53 scaling (Gainey, Hurvitz 51 (Malinow and Malenka 2002, Diering and Huganir 2018, Diaz-Alonso and Nicoll 2021, Bessa-Neto and<br>52 Choquet 2023, Stockwell, Watson et al. 2024). The GluA2 CTD plays an important role in synaptic<br>53 scaling (Gainey, Hur 53 scaling (Gainey, Hurvitz-Wolff et al. 2009, Ancona Esselmann, Diaz-Alonso et al. 2017), and the Gl<br>54 CTD regulates its subcellular distribution (Boehm, Kang et al. 2006, Luchkina, Coleman et al. 2017<br>55 However, it is 54 CTD regulates its subcellular distribution (Boehm, Kang et al. 2006, Luchkina, Coleman et al. 2017).<br>55 However, it is the GluA1 CTD which has received most of the attention. GluA1 CTD interactions with<br>56 Protein 4.1N 55 However, it is the GluA1 CTD which has received most of the attention. GluA1 CTD interactions with<br>56 Protein 4.1N and Sap97 can regulate intracellular AMPAR trafficking and synaptic content (Shen, Lia<br>57 et al. 2000, S For Frontein, it is the GluA<sub>1</sub> However, include intracellular AMPAR trafficking and synaptic content (Shen, Lia<br>57 et al. 2000, Sans, Racca et al. 2001, Kay, Tsan et al. 2022, Bonnet, Charpentier et al. 2023). During LT<br>5 Protein 4.1N and Sap97 can regulate intracellular AMPAR trafficking and synaptic content (Shen, Liang<br>et al. 2000, Sans, Racca et al. 2001, Kay, Tsan et al. 2022, Bonnet, Charpentier et al. 2023). During LTP,<br>the GluA1 CTD 58 the GluA1 CTD undergoes phosphorylation by CaMKII, PKC and PKA (Barria 1997, Hayashi 2000,<br>59 Esteban, Shi et al. 2003), and double phospho-null mutation of Serine 831 and 845 in the GluA1 CTD has<br>60 been shown to block 59 Esteban, Shi et al. 2003), and double phospho-null mutation of Serine 831 and 845 in the GluA1 C<br>60 been shown to block LTP (Lee, Takamiya et al. 2003). These and other studies support an essenti<br>61 for the GluA1 CTD in 59 Esteban, Shi et al. 2003), and doorse phospho-numeralism of Serine 832 and style fire side is the GluA1 CTD<br>60 been shown to block LTP (Lee, Takamiya et al. 2003). These and other studies support an essential role<br>62 CT for the GluA1 CTD in LTP. However, other evidence suggests a more nuanced role: i) the discovery that<br>CTD (Ser 831/ Ser 845)-phosphorylated GluA1 accounts for a negligible fraction of GluA1 at synapses *in*<br>vivo (Hosokawa, 61 for the GluA1 CTD in LTP. However, other evidence suggests a more nuanced role: i) the discovery that<br>62 CTD (Ser 831 / Ser 845)-phosphorylated GluA1 accounts for a negligible fraction of GluA1 at synapses *in*<br>63 vivo 62 CTD (Ser 831) Ser 845)-phosphorylated GluA1 accounts for a negligible fraction of GluA1 at synapses in<br>63 vivo (Hosokawa, Mitsushima et al. 2015) [although another study reported a sizable proportion of <sup>63</sup>vivo (Hosokawa, Mitsushima et al. 2015) [although another study reported a sizable proportion of

64 phosphorylated GluA1 (Diering, Heo et al. 2016)], ii) the finding that GluA1 lacking the PDZ-binding<br>65 motif traffics normally (Kim, Takamiya et al. 2005, Kerr and Blanpied 2012). iii), the demonstration that<br>66 CTD-l 166 CTD-lacking GluA1 can support basal AMPAR transmission and LTP at hippocampal CA3→CA1<br>167 synapses (Granger, Shi et al. 2013, Diaz-Alonso, Morishita et al. 2020, Watson, Pinggera et al. 2021).<br>168 Altogether, the emerg examples of the manner process of the support basel and the support of the Synapses (Granger, Shi et al. 2013, Diaz-Alonso, Morishita et al. 2020, Watson, Pinggera et al. 2014<br>68 Altogether, the emerging picture is that th examples (Cranger, Shi et al. 2021). Alto denote is that the presence of the GluA1 CTD is unlikely to be an absolute<br>for all and the emerging picture is that the presence of the GluA1 CTD is unlikely to be an absolute<br>for requirement for AMPAR-mediated synaptic transmission and LTP at CA1 PNs, where it may instead<br>TO play a more subtle role (Diaz-Alonso and Nicoll 2021, Bessa-Neto and Choquet 2023, Stockwell, Wat<br>T1 et al. 2024). However, t 69 play a more subtle role (Diaz-Alonso and Nicoll 2021, Bessa-Neto and Choquet 2023, Stockwell, Wat<br>et al. 2024). However, the contribution of the GluA1 CTD to synaptic transmission at other synapses,<br>especially excitator 20 play a more subtle role (Diaz-Alonso and Nicolation 2022) subtle role and Along Persons, et al. 2024). However, the contribution of the GluA1 CTD to synaptic transmission at other synapses,<br>22 especially excitatory syna

12 et al. 2024). However, the commodition of the Croins of the GluAnnimor of the GluAn especially excitatory synapses onto inhibitory neurons, remains largely unexplored.<br>The link between glutamatergic dysfunction and neur The link between glutamatery is a mannery performance in gray strangely in the link between glutamatergic dysfunction and neuropsychiatric disorders<br>74 (Coyle 2006, Lisman, Coyle et al. 2008, Tamminga, Southcott et al. 201 The link between greenhatergic dystement and neuroppy smaller are restrained to the detailshed<br>75 The link between greenings, Southcott et al. 2012). Specifically, the GRIA1 gene,<br>75 The link between is well-established as which encodes the GluA1 subunit, has been identified as a risk locus for schizophrenia in genome-wide<br>association studies (Ripke, O'Dushlaine et al. 2013, Schizophrenia Working Group of the Psychiatric<br>Genomics 2014), and 26 association studies (Ripke, O'Dushlaine et al. 2013, Schizophrenia Working Group of the Psychiatric<br>373 Genomics 2014), and postmortem analyses of individuals with schizophrenia show reduced levels of<br>38 GluA1 in severa 76 association studies (Ripke, O'Dushlaine et al. 2013, Schizophrenia Working Group of the Psychiatric<br>77 Genomics 2014), and postmortem analyses of individuals with schizophrenia show reduced levels of<br>78 GluA1 in several 1922 GluA1 in several brain regions, including the hippocampus (Harrison 1991, Eastwood 1996, Yonezaw.<br>1938 Tani et al. 2022). Excitatory synaptic plasticity, most importantly LTP, is disrupted in CA1 in GluA1 K<br>1938 Tani 59 GluA1 in several brain regions, including the hippocampus (Harrison 1991, Eastwood 1996, Yonezawa,<br>79 Tani et al. 2022). Excitatory synaptic plasticity, most importantly LTP, is disrupted in CA1 in GluA1 KO<br>78 Mice, whi 79 Tani et al. 2022). Excitency symptoms in novelty and salience processing and working memory<br>81 Teminiscent of some of the symptoms of schizoaffective disorders (Zamanillo D.; Sprengel and Kaiser<br>82 1999, Reisel, Bannerm 1980 mice, which also exhibit alternative materials, and salisfied processing and working memory,<br>81 miniscent of some of the symptoms of schizoaffective disorders (Zamanillo D.; Sprengel a<br>83 Barkus, Feyder et al. 2012, B 1989, Reisel, Bannerman et al. 2002, Bannerman, Deacon et al. 2004, Sanderson, Sprengel et al. 2011,<br>Barkus, Feyder et al. 2012, Barkus, Sanderson et al. 2014, Bannerman, Borchardt et al. 2018, Panayi,<br>Boerner et al. 2023) 83 Barkus, Feyder et al. 2012, Barkus, Sanderson et al. 2014, Bannerman, Borchardt et al. 2018, Panayi,<br>84 Boerner et al. 2023).<br>85 Using GluA1 CTD truncated (ACTD GluA1) mice, we found that the GluA1 CTD regulates

84 Boerner et al. 2023).<br>83 Boerner et al. 2023).<br>85 Using GluA1 CTD truncated ( $\triangle CTD$  GluA1) mice, we found that the GluA1 CTD regulates<br>86 AMPAR subunit protein levels and subcellular distribution. Interestingly, the CTD 85 Using GluA1<br>86 AMPAR subunit prot<br>87 GluA1-dependent fui 86 AMPAR subunit protein levels and subcellular distribution. Interestingly, the CTD is required for s<br>87 GluA1-dependent functions, most notably the regulation of the response to novelty as well as an<br>88 and despair-rela 87 GluA1-dependent functions, most notably the regulation of the response to novelty as well as anxiety<br>88 and despair-related behaviors, but not for GluA1-dependent memory processes. Our results suggest<br>89 that the GluA1 and despair-related behaviors, but not for GluA1-dependent memory processes. Our results suggest<br>that the GluA1 CTD modulates AMPAR synaptic transmission in a subunit composition-dependent anc<br>ell type-specific manner. Alt 88 that the GluA1 CTD modulates AMPAR synaptic transmission in a subunit composition-dependent are cell type-specific manner. Altogether, this study expands our understanding of the cell-type specific<br>81 regulation of exci 1988 that the GluAn Contract that the GluAn Compared that the GluAn Component and Selection-dependent and selection-<br>1988 that the cell-type specific<br>1988 that into the neurobiological mechanisms<br>1988 regulating the putati 91 regulation of excitatory synaptic transmission and sheds light into the neurobiological mechanisms<br>92 regulating the putative schizophrenia risk-associated GluA1.<br>93 Materials and Methods 1991 regulating the putative schizophrenia risk-associated GluA1.<br>93 Materials and Methods<br>93 Materials and Methods

# 92 regulating the putative schizophrenia risk-associated GluA1.<br>93 Materials and Methods 93 Materials and Methods

95 And Animals<br>96 the Unive<br>97 in a 12-he<br>98 homozyg 1999 The University of California, Irvine (protocol numbers AUP-20-156; AUP-23-076). Mice were maintaine<br>97 In a 12-hour light/dark schedule and had access to food and water, ad libitum. Generation of<br>98 Interval Animal A 97 in a 12-hour light/dark schedule and had access to food and water, ad libitum. Generation of<br>98 homozygous HA-ΔCTD GluA1 knock-in (referred to as ΔCTD GluA1) mice was previously described<br>99 (Diaz-Alonso, Morishita et 98 homozygous HA-ΔCTD GluA1 knock-in (referred to as ΔCTD GluA1) mice was previously des<br>99 (Diaz-Alonso, Morishita et al. 2020). Genotyping was carried out by TransnetYX Inc.<br>00 <u>Biochemistry</u> 99 (Diaz-Alonso, Morishita et al. 2020). Genotyping was carried out by TransnetYX Inc.<br>00<br>01 Biochemistry WT and ΔCTD GluA1 mouse forebrains were dissected and homogenized in Synaptic Protei

99 (Diaz-Alonso, Morishita et al. 2020). Genotyping was carried out by TransnetYX Inc.<br>100<br>101 <u>Biochemistry</u><br>102 WT and ΔCTD GluA1 mouse forebrains were dissected and homogenized in Synaptic Protein<br>103 Extraction Reagen 102 WT ar<br>
103 Extraction Rea<br>
104 #1183617000:<br>
105 (Bernard, Exp 104 #11836170001). Synaptosomes were then obtained following manufacturer's instructions, as in<br>105 (Bernard, Exposito-Alonso et al. 2022). For immunoblot, whole brain lysates and synaptosomal<br>106 fractions were denatured 104 #11836170001). Synaptosomes were then obtained following manufacturer's instructions, as in<br>105 (Bernard, Exposito-Alonso et al. 2022). For immunoblot, whole brain lysates and synaptosomal<br>106 fractions were denatured 105 (Bernard, Exposito-Alonso et al. 2022). For immunoblot, whole brain lysates and synaptosomal<br>106 fractions were denatured at 95 °C for 5 min. in Laemmli sample buffer (Sigma, #S-3401) and pro<br>107 for SDS-PAGE. Immuno-B 106 fractions were denatured at 95 °C for 5 min. in Laemmli sample buffer (Sigma, #S-3401) and pro<br>107 for SDS-PAGE. Immuno-Blot PVDF membranes (Bio-Rad, #1620177) were blocked with 5% blot<br>108 grade nonfat milk (Lab Scien 107 for SDS-PAGE. Immuno-Blot PVDF membranes (Bio-Rad, #1620177) were blocked with 5% blotting<br>108 grade nonfat milk (Lab Scientific, #Mo841) in tris-buffered saline with 0.1% tween 20 (Sigma-Aldrich,<br>109 #P1379). The foll grade nonfat milk (Lab Scientific, #Mo841) in tris-buffered saline with 0.1% tween 20 (Sigma-Aldrich<br>109 #P1379). The following primary antibodies were used at a 1:1000 dilution: guinea pig anti-GluA2 CTD<br>110 (Synaptic Sys 109 #P1379). The following primary antibodies were used at a 1:1000 dilution: guinea pig anti-GluA2 CTD<br>110 (Synaptic Systems, #182 105), mouse anti-GluA1 ATD (Cell Signaling, #13185S), rabbit anti-GluA3<br>111 (Alomone Labs, 110 (Synaptic Systems, #182 105), mouse anti-GluA1 ATD (Cell Signaling, #13185S), rabbit anti-GluA3<br>111 (Alomone Labs, #AGC-010), rabbit anti-GluA4 (Cell Signaling, # 8070), mouse anti PSD-95 (Synaptic<br>112 systems, #124 01 110 (Synaptic Systems, #182 105), mouse anti-GluA1 ATD (Cell Signaling, #13185S), rabbit anti-GluA3<br>111 (Alomone Labs, #AGC-010), rabbit anti-GluA4 (Cell Signaling, # 8070), mouse anti PSD-95 (Synaptic<br>112 systems, #124 01 112 systems, #124 011) and mouse anti-tubulin (Millipore-Sigma, #T9026). HRP-conjugated secondary<br>113 antibodies raised against the appropriate species were used: anti-rabbit IgG (Vector laboratories #PI-<br>114 1000), anti-m 113 antibodies raised against the appropriate species were used: anti-rabbit IgG (Vector laboratories #P<br>114 1000), anti-mouse IgG (Vector laboratories #PI-2000), and anti-guinea pig IgG (Millipore Sigma<br>115 #AP108P). Mem 114 and the anti-rabbit is a propriate species were vector and the anti-rabbit is also anti-rabbit is also and<br>115 #AP108P). Membranes were incubated with ClarityTM Western ECL (BioRad, #170-5060). When<br>116 meeded, membra 115 #AP108P). Membranes were incubated with ClarityTM Western ECL (BioRad, #170-5060). Whe<br>116 meeded, membranes were incubated in stripping buffer containing Guanidine HCl and β-<br>117 mercaptoethanol and triton x-100 in p 116 meeded, membranes were incubated in stripping buffer containing Guanidine HCl and β-<br>117 mercaptoethanol and triton x-100 in pH 7.5 Tris HCl buffer, with gentle agitation at RT for 30 min.<br>118 Following incubation, me needed, membranes were incubated in stripping buffer containing Guanidine HCl and β-<br>117 mercaptoethanol and triton x-100 in pH 7.5 Tris HCl buffer, with gentle agitation at RT fo<br>118 Following incubation, membranes were 118 Following incubation, membranes were rinsed, blocked and incubated with another Ab.<br>119 <u>Confocal microscopy and image analysis</u><br>121 MT and ΔCTD GluA1 brain samples were sectioned (40 μm, coronal) following fixation i 119 Following incubation, membranes were missed, broken and incubated with another Ab.<br>120 Fonfocal microscopy and image analysis<br>121 For and ΔCTD GluA1 brain samples were sectioned (40 μm, coronal) following fix<br>122 Fora 119<br>120 120 Confocal microscopy and image analysis<br>121 WT and  $\Delta$ CTD GluA1 brain samples were sectioned (40 µm, coronal) following fixation in 4%<br>122 paraformaldehyde. After blocking with 5% swine serum (Jackson Immuno Research, 122 paraformaldehyde. After blocking with 5% swine serum (Jackson Immuno Research, #014-000-121) a<br>123 2% BSA (Cell Signaling, #9998S) in permeabilizing conditions (0.1% Triton X-100, Sigma-Aldrich,<br>124 #T8787), samples w

- 2% BSA (Cell Signaling, #9998S) in permeabilizing conditions (o.1% Triton X-100, Sigma-Aldrich,<br>124 #T8787), samples were incubated overnight at 4° C with the following primary antibodies: rabbit anti-<br>125 GluA1 ATD (Cell 124 #T8787), samples were incubated overnight at 4° C with the following primary antibodies: rabbit a<br>125 GluA1 ATD (Cell signaling, #13185, 1:500), guinea pig anti-GluA2 (Synaptic Systems, #182 105, 1:5<br>125 GluA1 ATD (Cel
- 125 GluA1 ATD (Cell signaling, #13185, 1:500), guinea pig anti-GluA2 (Synaptic Systems, #182 105, 1:500), and<br>125 GluA1 ATD (Cell signaling, #13185, 1:500), guinea pig anti-GluA2 (Synaptic Systems, #182 105, 1:500), 125 Gluan 125 Gluan and the United States of the United States pig anti-Gluan (Synaptic Systems), 1:500, 1:50<br>5. 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:5000, 1:500, 1:50<br>5

127 rabbit anti-GluA3 (Abcam, #AB190289, 1:500) and mouse anti PSD-95 (Synaptic Systems, #124 011, 1:500) followed by incubation with Alexa 488 goat anti-mouse (Life Technologies, #A-11001, 1:500),<br>Alexa 594 goat anti-rabb 128 1:500) followed by incubation with Alexa 488 goat anti-mouse (Life Technologies, #A-11001, 1:500),<br>129 Alexa 594 goat anti-rabbit (Life Technologies, #A11012, 1:500), Alexa 647 goat anti-rabbit (Life<br>130 Technologies, 129 Alexa 594 goat anti-rabbit (Life Technologies, #A11012, 1:500), Alexa 647 goat anti-rabbit (Life Technologies, #A21245, 1:500) and Alexa 568 goat anti-guinea pig (Life Technologies, #A11075, 1:50<br>131 secondary antibodi 130 Technologies, #A21245, 1:500) and Alexa 568 goat anti-guinea pig (Life Technologies, #A11075<br>131 secondary antibodies for 2 hours at RT. Slides were mounted with ProLong Gold Antifade Reag<br>132 DAPI (Cell Signaling Tech Technologies, #A21245, 1:500) and Alexa 568 goat anti-guinea pig (Life Technologies, #A11075, 1:500)<br>131 secondary antibodies for 2 hours at RT. Slides were mounted with ProLong Gold Antifade Reagent with<br>132 DAPI (Cell Si

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132 DAPI (Cell Signaling Technology, #89615).<br>133 Secondary and Technology, #89615).<br>134 Confocal images were collected using a Leica Sp8 confocal microscope (Leica Microsystems,<br>135 Wetzlar, Germany). Dorsal hippocampus f 133<br>134 Confocal images were collected usi<br>135 Wetzlar, Germany). Dorsal hippocampus fie<br>136 radiatum (SR) were acquired using a 63x oil 135 Wetzlar, Germany). Dorsal hippocampus field CA1 images including stratum pyramidale and stratum<br>136 radiatum (SR) were acquired using a 63x oil objective as a series of 20 z-steps, with a z-step size of 1 μ<br>137 at a r 136 radiatum (SR) were acquired using a 63x oil objective as a series of 20 z-steps, with a z-step size of 1 µ<br>137 at a resolution of 1024 x 1024 pixels, and a scanning frequency of 400 Hz. The optical resolution (voxe<br>138 137 at a resolution of 1024 x 1024 pixels, and a scanning frequency of 400 Hz. The optical resolution (voxel<br>138 size) per image was 180 nm in the xy-plane and 1.03 μm in the z-plane. Analysis of synaptic localization<br>139 138 size) per image was 180 nm in the xy-plane and 1.03 µm in the z-plane. Analysis of synaptic localization<br>139 was performed using Imaris 9.9.1 (Bitplane, South Windsor, CT, USA) and MatLab Runtime R2022b<br>140 (Mathworks, 139 was performed using Imaris 9.9.1 (Bitplane, South Windsor, CT, USA) and MatLab Runtime R2022b<br>140 (Mathworks, Natick, MA, USA), as previously described (Bemben, Sandoval et al. 2023). Briefly, the<br>141 "Spots" tool was 140 (Mathworks, Natick, MA, USA), as previously described (Bemben, Sandoval et al. 2023). Briefly, the<br>141 "Spots" tool was utilized to assign representative three-dimensional ellipsoid shapes to individual<br>142 synaptic-li 141 "Spots" tool was utilized to assign representative three-dimensional ellipsoid shapes to individual<br>142 synaptic-like GluA1, GluA2, GluA3 and PSD-95 puncta. Then "Background Subtraction" was applied<br>143 deduce backgrou 142 synaptic-like GluA1, GluA2, GluA3 and PSD-95 puncta. Then "Background Subtraction" was applie<br>143 reduce background signal. A region of interest (ROI) was created to restrict the colocalization<br>144 and unantification t 143 reduce background signal. A region of interest (ROI) was created to restrict the colocalization<br>144 quantification to CA1 SR. The number of spots was adjusted qualitatively using the automatically<br>145 generated and int 144 quantification to CA1 SR. The number of spots was adjusted qualitatively using the automatical<br>145 generated and interactive "Quality" filter histogram to select dense signal while excluding pur<br>146 to be background si 145 generated and interactive "Quality" filter histogram to select dense signal while excluding puncta<br>146 to be background signal. To ensure an accurate spot segmentation of the underlying puncta<br>147 determined by size, t 146 to be background signal. To ensure an accurate spot segmentation of the underlying puncta<br>147 determined by size, the "Different Spots Sizes" selection was utilized, adjusting contrast with the<br>148 "Local Contrast" too 147 determined by size, the "Different Spots Sizes" selection was utilized, adjusting contrast with<br>
148 "Local Contrast" tool. The histogram was adjusted to accurate puncta coverage. Spots were<br>
149 rendered. Once optimal 148 "Local Contrast" tool. The histogram was adjusted to accurate puncta coverage. Spots were then<br>149 mendered. Once optimal settings for each of these parameters were established for the GluA1, Glu<br>150 GluA3, or PSD-95 c "Local Contrast" tool. The histogram was adjusted to accurate puncta coverage. Spots were then<br>149 rendered. Once optimal settings for each of these parameters were established for the GluA1, GluA2,<br>150 GluA3, or PSD-95 ch Threshold for colocalization was established at 0.7  $\mu$ m from the center of neighboring puncta.<br>Electrophysiology 151 Threshold for colocalization was established at 0.7 µm from the center of neighboring puncta.<br>152 Electrophysiology<br>154 Whole-cell patch-clamp recordings were obtained from DG GCs or GABAergic interneurons

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152<br>152 Electrophysiology<br>154 Whole-cell patch-clamp recordings were obtained from DG GCs or GABAergic internet<br>155 (INs) using acute brain slices from 2-6 months-old male and female mice. 300 μm horizontal sli 154 Whole-cell<br>155 (INs) using acute b<br>156 obtained in ice-col<br>157 NaH<sub>2</sub>PO<sub>4</sub>, 30 NaHC 155 (INs) using acute brain slices from 2-6 months-old male and female mice. 300 µm horizontal slices w<br>156 obtained in ice-cold, oxygenated NMDG recovery solution containing (in mM): 92 NMDG, 2.5 KCl, 1.<br>157 NaH<sub>2</sub>PO<sub>4</sub>, 156 obtained in ice-cold, oxygenated NMDG recovery solution containing (in mM): 92 NMDG, 2.5 KCl, 1.25<br>157 NaH<sub>2</sub>PO<sub>4</sub>, 30 NaHCO<sub>3</sub>, 20 HEPES, 25 glucose, 2 thiourea, 5 Na-ascorbate, 3 Na-pyruvate, 0.5 CaCl<sub>2</sub>•2 156 obtained in ice-cold, oxygenated NMDG recovery solution containing (in mM): 92 NMDG, 2.5 KCl, 1.2<br>157 NaH<sub>2</sub>PO<sub>4</sub>, 30 NaHCO<sub>3</sub>, 20 HEPES, 25 glucose, 2 thiourea, 5 Na-ascorbate, 3 Na-pyruvate, 0.5 CaCl,•2  $157$  NaH<sub>2</sub>PO<sub>4</sub>, 30 NaHCO<sub>3</sub>, 20 HEPES, 25 glucose, 2 thiodica<sub>,</sub> 3 Na-ascorbate, 3 Na-pyruvate, 0.5 CaCl<sub>2</sub> –

159 included for at least 30 min. at 34°C in artificial cerebrospinal fluid (aCSF) composed of (in mM): 119<br>160 NaCl, 2.5 KCl, 1 NaH<sub>2</sub>PO<sub>4</sub>, 26.2 NaHCO<sub>3</sub>, 11 glucose, 2.5 and 1.3 MgSO<sub>4</sub>. aCSF was bubbled with 95% C<br>161 160 NaCl, 2.5 KCl, 1 NaH<sub>2</sub>PO<sub>4</sub>, 26.2 NaHCO<sub>3</sub>, 11 glucose, 2.5 and 1.3 MgSO<sub>4</sub>. aCSF was bubbled with 95% (and 5% CO<sub>2</sub>. Osmolarity was adjusted to 307-310 mOsm. For recordings, slices were perfused with aC<br>162 containi and 5% CO<sub>2</sub>. Osmolarity was adjusted to 307-310 mOsm. For recordings, slices were perfused with aCSF<br>161 and 5% CO<sub>2</sub>. Osmolarity was adjusted to 307-310 mOsm. For recordings, slices were perfused with aCSF<br>162 containin 162 containing 100 μM picrotoxin to block GABA A-mediated responses. Recording pipettes (3-6 MΩ) were<br>163 filled with internal solution containing (in mM): 135 CsMeSO<sub>4</sub>, 8 NaCl, 10 HEPES, 0.3 EGTA, 5 QX-314, 4<br>164 Mg-AT 163 filled with internal solution containing (in mM): 135 CsMeSO<sub>4</sub>, 8 NaCl, 10 HEPES, 0.3 EGTA, 5 OX-314, 4<br>164 Mg-ATP, 0.3 Na-GTP, and 0.1 spermine. Osmolarity was adjusted to 290-292 mOsm, and pH at 7.3–7.4.<br>165 Membran 164 Mg-ATP, o.3 Na-GTP, and o.1 spermine. Osmolarity was adjusted to 290-292 mOsm, and pH at 7.3–7.4.<br>165 Membrane holding current, input resistance and pipette series resistance were monitored throughout<br>166 experiments. 165 Membrane holding current, input resistance and pipette series resistance were monitored throughout<br>166 experiments. Data were gathered through a IPA2 amplifier/digitizer (Sutter Instruments), filtered at 5<br>167 kHz, and 166 experiments. Data were gathered through a IPA2 amplifier/digitizer (Sutter Instruments), filtered at 5<br>167 kHz, and digitized at 10 kHz. Series compensation was not performed during data acquisition. For<br>168 evoked EPS 167 kHz, and digitized at 10 kHz. Series compensation was not performed during data acquisition. For<br>168 evoked EPSC recordings, a tungsten bipolar electrode was placed in the DG stratum moleculare (SM),<br>169 thereby stimul 168 evoked EPSC recordings, a tungsten bipolar electrode was placed in the DG stratum moleculare (S<br>169 thereby stimulating perforant path (PP) inputs onto DG GCs. Electric pulses were delivered at 0.2 k<br>170 AMPAR EPSCs we 169 thereby stimulating perforant path (PP) inputs onto DG GCs. Electric pulses were delivered at 0.2 Hz.<br>170 AMPAR EPSCs were obtained while holding the cell at -70 mV; NMDAR currents were obtained at +40<br>171 mV. The peak 170 AMPAR EPSCs were obtained while holding the cell at -70 mV; NMDAR currents were obtained at +4c<br>171 mV. The peak evoked AMPAR response and NMDAR component 100 ms after the stimulation artifact<br>172 (to avoid contributio 171 mV. The peak evoked AMPAR response and NMDAR component 100 ms after the stimulation artifact<br>172 (to avoid contribution of the AMPAR EPSC) were used to calculate the AMPAR/NMDAR ratio. In paired<br>173 pulse ratio (PPR) e 172 (to avoid contribution of the AMPAR EPSC) were used to calculate the AMPAR/NMDAR ratio. In paired<br>173 pulse ratio (PPR) experiments, stimulation was delivered at an inter-stimulus interval of 50 ms. PPR was<br>174 calcula 173 pulse ratio (PPR) experiments, stimulation was delivered at an inter-stimulus interval of 50 ms. PPR was<br>174 calculated by dividing the second EPSC by the first. Input/Output (I/O) relationship was assessed by<br>175 sti pulse ratio (PPR) experiments, stimulation was delivered at an inter-stimulus interval of 50 ms. PPR w<br>174 calculated by dividing the second EPSC by the first. Input/Output (I/O) relationship was assessed by<br>175 stimulati 178 comprised of 5 bursts of spikes (4 pulses at 100 Hz) at 5 Hz applied to the SC fibers at 0.1 Hz, paired with 177 using a theta-burst stimulation (TBS) induction protocol, consisting in four trains of TBS, each train<br>178 comprised of 5 bursts of spikes (4 pulses at 100 Hz) at 5 Hz applied to the SC fibers at 0.1 Hz, paired<br>179 pos 177 using a theta-burst stimulation (TBS) induction protocol, consisting in four trains of TBS, each train<br>178 comprised of 5 bursts of spikes (4 pulses at 100 Hz) at 5 Hz applied to the SC fibers at 0.1 Hz, paired w<br>179 p 178 comprised of 5 bursts of spikes (4 pulses at 100 Hz) at 5 Hz applied to the SC fibers at 0.1 Hz, paired<br>179 postsynaptic depolarization at omV, as in (Traunmuller, Gomez et al. 2016). Statistical analysis was<br>180 perfo 179 postsynaptic depolarization at omV, as in (Traunmuller, Gomez et al. 2016). Statistical analysis was<br>180 performed at min. 45 after induction. Recordings from cells lost at any point between induction and the<br>181 end o 180 performed at min. 45 after induction. Recordings from cells lost at any point between induction and<br>181 end of the experiment (min. 40) were considered until that point.<br>182 Electrophysiology data was gathered and anal 180 performed at min. 45 after induction. Recordings from cells lost at any point between induction and the<br>181 end of the experiment (min. 40) were considered until that point.<br>182 Electrophysiology data was gathered and

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182 Electrophysiology data was gathered and analyzed using<br>184 Igor Pro (Wavemetrics).<br>185 184 Electrophysiology data was gathered and analyzed using Sutterpatch (Sutter Instruments) and<br>184 Electrophysiology<br>186 <u>Behavior</u> Mice were group-housed with littermates. Mice were handled for 1 min for 4 consecutive da

185<br>186 <u>Behavior</u><br>187 Mice were group<br>188 prior to all behavioral tes 187 M<br>188 prior to al<br>189 the behav 188 prior to all behavioral testing. At the beginning of each testing day, mice were allowed to acclimate to<br>189 the behavior room for at least 30 min. before the start of the experiment. Behavioral chambers and<br>189 the be 189 the behavior room for at least 30 min. before the start of the experiment. Behavioral chambers and<br>189 the behavior room for at least 30 min. before the start of the experiment. Behavioral chambers and 189 the behavior room for at least 30 min. before the start of the start of the experiment. Behavioral chambers and<br>International chambers and the experiment. Behavioral chambers and the experiment. Behavioral chambers and

190 objects were cleaned and de-odorized between mice. Behavioral scoring was done by a researcher blind<br>191 to the genotype. Initial behavioral assessments performed at the Gladstone Institute Behavior Core<br>192 used male 191 to the generyper initial behavior a decession integer on the Gladstone Institute Behavior 2016<br>192 used male mice only. Subsequent studies at UC Irvine included both male and female mice, and data<br>194 Open Field (OF):

192 used male mice only. Subsequent states at UC IRMS matches at UC IRMS and CHIRC MIS (1920)<br>193 from both sexes were pooled.<br>195 *Open Field (OF)*: Mice were placed at the center of an OF arena and allowed to explore for 194<br>195 *Open Field (OF)*: Mice were pla<br>196 Gladstone experiments, activit<br>197 Field/Open Field Photobeam A 195Open Field (OF): Mice were placed at the center of an OF arena and allowed to explore for 15 min. In the Gladstone experiments, activity was recorded in a clear acrylic (41 x 41 x 30 cm) chamber using a Flex-<br>Field/Open 197 Field/Open Field Photobeam Activity System (San Diego Instruments, San Diego, CA) with two 16 x 1<br>198 photobeam arrays that automatically detected horizontal and vertical (rearing) movements. Rearings<br>199 were also qua 198 photobeam arrays that automatically detected horizontal and vertical (rearing) movements. Rearings<br>199 were also quantified. In the UCI experiments, locomotor activity was recorded by an overhead camera<br>100 in a white, 198 photobeam arrays that automatically detected horizontal and vertical (rearing) movements. Rearings<br>199 were also quantified. In the UCI experiments, locomotor activity was recorded by an overhead camera<br>100 in a white, 199 methods quantified in the Interpendent of activity was recorded was analyzed using a tracking<br>
1990 in a white, 30 x 23 x 23 cm plastic chamber and total distance traveled was analyzed using a tracking<br>
1991 analysis c 201 in a which young on plastic chamber and total and total distance analyzed using a trading<br>201 in analysis code written in MatLab (Github: https://github.com/HanLab-OSU/MouseActivity). The cent<br>203 in analysis code writ

202 analysis code written in Materia (Cithub: Materia Materia), Materia (Cithub: 1914), Materia (2014)<br>203<br>204 *Object Location Memory (OLM) task*: Mice were habituated to a white Plexiglas chamber (30 x 23 x 23 x<br>205 cm) 203<br>204 *Object Location Memory (OLM) task*: Mice were habituated to a white Plexiglas chamber (30 x 23 x 23 x<br>205 cm) for 5 min. daily for 4 days. On the training day, mice were placed in the chamber with two identical<br>20 203 204 *Doject Location Memory (OLM) task:* Mice were habituated to a white Plexigias chamber (30 x 23 x 23 x<br>205 cm) for 5 min. daily for 4 days. On the training day, mice were placed in the chamber with two identica<br>206 obj 206 objects and allowed to explore them for 10 min. On the test day, 24 hours later, mice were placed in the<br>207 chamber with either object displaced to a different location and allowed to explore the arena for 5 min.<br>208 207 chamber with either object displaced to a different location and allowed to explore the arena for 5 min.<br>208 Object identity was counterbalanced between genotypes. The animal's behavior was recorded using an<br>209 overhe 208 Object identity was counterbalanced between genotypes. The animal's behavior was recorded using an<br>209 overhead camera and object exploration time scored using the criteria described by (Vogel-Ciernia and<br>210 Wood 2014 209 overhead camera and object exploration time scored using the criteria described by (Vogel-Ciernia and Wood 2014). Discrimination index (DI) was calculated as follows: (Novel Object Time – Familiar Object Time) / (Novel overhead camera and object exploration time scored using the criteria described by (Vogel-Ciernia and<br>210 Wood 2014). Discrimination index (DI) was calculated as follows: (Novel Object Time – Familiar Object<br>211 Time) / (N 211 Time) / (Novel Object Time + Familiar Object Time) x 100. A DI score of +20 or greater was determined<br>212 as learning. DI was calculated for both training and test day. Exclusion criteria: Mice that scored ±20<br>213 pref 212 as learning. DI was calculated for both training and test day. Exclusion criteria: Mice that scored ±20 preference for an individual object on training day and mice that explored the objects less than 3 seconds were ex 213 preference for an individual object on training and anice that explored the objects less than 3<br>214 seconds were excluded from analysis.<br>215 Novel Objection Recognition (NOR) task: Mice handling and habituation were as

214 preference for an individual only is an individual only that the object on the object only is<br>215 *Novel Objection Recognition (NOR) task*: Mice handling and habituation were as described for the task. On training day, 215<br>216 Novel Objection Recognition (NOR) task<br>217 task. On training day, mice were place<br>218 explore them for 10 min. The following 217 task. On training day, mice were placed in the chamber with two identical objects and allowed to<br>218 task. On training day, mice were placed in the chamber with two identical objects and allowed to<br>218 explore them for 218 explore them for 10 min. The following day (test day), mice were placed back in the chamber with<br>219 familiar and one novel object and allowed to explore for 5 min. The identity of the novel object was<br>220 counterbalan explore them for 10 min. The following day (test day), mice were placed back in the chamber with of the miliar and one novel object and allowed to explore for 5 min. The identity of the novel object was counterbalanced bet counterbalanced between genotypes. Discrimination index was calculated as described for OLM. 220 counterbalanced between genotypes. Discrimination index was calculated as described for OLM.

Forced Alternation Y-maze: The forced alternation task was performed using an opaque Plexiglas Y-<br>223 maze. Each arm was 36 x 21 x 10 cm. On the training trial, mice were placed into a starting arm, facing<br>224 the center o 225 blocked. After an inter-trial interval of 1 min., mice were placed back in the maze at the same starting<br>226 arm and allowed to explore all three arms for 5 min. The starting arm and blocked arm were<br>227 counterbalance 226 arm and allowed to explore all three arms for 5 min. The starting arm and blocked arm were<br>1977 counterbalanced across mice. The maze was cleaned and deodorized with 70% ethanol between trials.<br>1978 Total number of arm 226 arm and allowed to explore all three arms for 5 min. The starting arm and blocked arm were<br>227 counterbalanced across mice. The maze was cleaned and deodorized with 70% ethanol between trials<br>228 Total number of arm cr 227 counterbalanced across mice. The maze was cleaned and deodorized with 70% ethanol betw<br>228 Total number of arm crossings and time spent in each arm was scored using a mouse trackin<br>229 (Any-Maze, Stoelting Co). Mice we 228 Total number of arm crossings and time spent in each arm was scored using a mouse tracking software<br>229 (Any-Maze, Stoelting Co). Mice were required to enter an arm with at least 2/3 of its body to be<br>230 considered a 229 (Any-Maze, Stoelting Co). Mice were required to enter an arm with at least 2/3 of its body to be<br>230 considered a crossing. DI was calculated as Novel Arm Time / (Novel Arm Time + Non-Starting Arm) x<br>231 100 (Wolf et a (Any-Maze, Stoelting Co). Mice were required to enter an arm with at least 2/3 of its body to be<br>230 considered a crossing. DI was calculated as Novel Arm Time / (Novel Arm Time + Non-Starting Arm) x<br>231 100 (Wolf et al., 234 valls, 38 x 5 cm) and two closed arms (with 16.5 cm tall walls), the intersection of the arms was 5 x 5 cm, 232<br>233 Elevated Plus Maze: Mi<br>234 walls, 38 x 5 cm) and tw<br>235 and the entire maze is 6 232 233 Elevated 7 ios muze: Mice were placed in the center of an elevated maze with two open arms (without walls,  $38 \times 5$  cm) and two closed arms (with 16.5 cm tall walls), the intersection of the arms was  $5 \times 5$  cm<br>235 an 235 and the entire maze is elevated 77.5 cm above the ground (Hamilton-Kinder, Poway, CA). Total time<br>236 spent and distance traveled in each arm were measured across the 10-min session.<br>237 Forced Swim Test: Mice were ind 236 and the entire masses of entire may give the ground (Hamilton-Miller, Pount, Cali, Poway, 2006)<br>236 and the entire may be the ground (Hamilton-Kinder).<br>238 *Forced Swim Test:* Mice were individually placed in a clear p 236 spent and distance traveled in each arm were measured across the 10-min session.<br>237 *Forced Swim Test: Mice were individually placed in a clear plastic cylinder (25.5 cm diameter x 23 cm<br>139 height), filled with water* 237 238 Forced Swim Fest: Mice were individually placed in a clear plastic cylinder (25.5 cm diameter x 23 cm<br>239 height), filled with water at 24°C, for 5 min. The total time spent immobile in the last 3 min. of the ta<br>241 Li 241<br>242 height/Dark Transition Test: The light-dark apparatus consisted of an opaque acrylic box (42 x 21 x 25 cm)<br>243 divided into two compartments (2/3 light, 1/3 dark) with a small opening connecting the two chambers. 241 Was scored. Floating, balancing and the summing were considered immobility (can, Dao et al. 2021).<br>242 Uight/Dark Transition Test: The light-dark apparatus consisted of an opaque acrylic box (42 x 21 x 25 cm<br>243 The li 242 242 *Light/Dark Transition Test:* The light-dark apparatos consisted of an opaque acrylic box (42 x 21 x 25 cm)<br>243 divided into two compartments (2/3 light, 1/3 dark) with a small opening connecting the two chambers.<br>244 244 The light compartment was made of opaque white walls and lit by an overhead lamp, while the dark<br>245 compartment was unlit and made of black non-transparent acrylic walls. Mice were first placed in the<br>246 light compar 245 compartment was unlit and made of black non-transparent acrylic walls. Mice were first placed in the light compartment and allowed to freely explore both chambers for 10 min. The time spent in each chamber, number of c 246 light compartment and allowed to freely explore both chambers for 10 min. The time spent in each<br>247 chamber, number of crossings, and the latency to enter the dark chamber was recorded using Any-<br>248 Maze (Stoelting C 247 Islam comparison and allowed to the symptoms of the free to free limit the allowed to free to free to free<br>248 Islam Contact to free to free to free to free the dark chamber was recorded using Any-<br>249 Contextual Fear

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248 Maze (Stoelting Co.).<br>248 Maze (Stoelting Co.).<br>250 *Contextual Fear Paradigm*: Fear conditioning experiments were conducted using a Med Associates<br>251 VideoFreeze system. The fear conditioning chamber (24 x 30.5 x 21. 249<br>250 Contextual Fear Parad<br>251 VideoFreeze system.<br>252 attenuating shell (63.

250Contextual Fear Paradigm: Fear conditioning experiments were conducted using a Med Associates<br>251Contextual Fear Paradigm: Fear conditioning chamber (24 x 30.5 x 21.5 cm) sits inside a sound<br>252Contenuating shell (63.5 252 attenuating shell (63.5 x 75 x 35.5 cm, Med Associates, Fairfax, Vermont). On the training day<br>253 were placed into a conditioning chamber and four-foot shocks (0.45 mA, 2s) were delivered a<br>253 were placed into a cond 252 attenuating shell (63.5 x 75 x 35.5 cm, Med Associates, Fairfax, Vermont). On the training day, mice<br>253 were placed into a conditioning chamber and four-foot shocks (0.45 mA, 2s) were delivered at min. 5, 7,

253 were placed into a conditioning chamber and four-foot shocks (0.45 mA, 2s) were delivered at min. 5, 7,

9, and 11 of a 13-minute training period. The following day (context recall test), mice were exposed to<br>255 the conditioned context in the absence of foot shocks for 10 min. Fear generalization was assessed 48<br>256 hours af 256 hours after the initial training in a different context in a 10 min. Session. In this generalization context,<br>257 tactile, visual, auditory, and olfactory stimuli were all distinct from the training context. Freezing<br>2 257 hours are made a lamps in a distinct content content context in any generalization context.<br>258 behavior was measured at baseline and during conditioning, the contextual recall test, and the generalization test.<br>259 ge 258 behavior was measured at baseline and during conditioning, the contextual recall test, and the<br>259 generalization test.<br>260 For the pre-exposure experiment, on the pre-exposure day mice were placed into the 259 behavior was measured at baseline and during conditioning, the conditioning conditioning chamber for 30 min., with no foot shocks. 24 hours later, on conditioning day, mich the conditioning chamber for 30 min., with no 259 generalization test. 260<br>261 262 conditioning chamber for 30 min., with no foot shocks. 24 hours later, on conditioning day, mice were placed back into a conditioning chamber for 13 min, with four foot shocks (o.6mA, 2s) delivered 5, 7, 9, and 11. 24 conditioning chamber for 30 min., with no foot shocks. 24 hours later, on conditioning day, mice were<br>263 placed back into a conditioning chamber for 13 min, with four foot shocks (o.6mA, 2s) delivered at min.<br>264 5, 7, 9, 264 5, 7, 9, and 11. 24 hours later, on the third day, mice were placed into the conditioned context in the<br>265 absence of foot shocks for a context recall test, where freezing was measured across a 10 min period.<br>266 The 265 absence of foot shocks for a context recall test, where freezing was measured across a 10 min period<br>266 The chamber context remained the same over all three days.<br>267 Shock reactivity was measured during training by t 266 The chamber context remained the same over all three days.<br>267 Shock reactivity was measured during training by the VideoFreeze system and expressed as the max motion index. 267<br>268 Shock reactivity was measured during training by the<br>269 max motion index.<br>270 269 Show max motion index.<br>269 Show reaction index.<br>271 *Hot plate test*: Hot plate nociception was measured on a black anodized, aluminum plate (IITC Life<br>272 Science, Woodland Hills, CA) heated to 52°C. Latency to withdr 270<br>271 Mot plate test: Hot<br>272 Science, Woodland<br>273 was measured to th 270<br>271 271 The plate test: Hot plate nociception was measured on a black anodized, aluminum plate (if it clife)<br>272 Science, Woodland Hills, CA) heated to 52°C. Latency to withdraw one of the hind paws from the p<br>273 Stereotaxic 272 Science, Woodland Hills, CA) heated to 52°C. Latency to minimum one of the hims pane nonline plate<br>273 Stereotaxic Viral Injection<br>275 Stereotaxic Viral Injection<br>276 Mice were anesthetized using isoflurane and bilater 274<br>275 Stereotaxic Viral Injection<br>276 Mice were anesthetized using isoflurane and bilateral<br>277 hippocampal DG field (AP: -3.39, ML: ±2.50, DV: -3.4, 274<br>275 276 Mice were anesthetized us<br>277 hippocampal DG field (AP:<br>278 (8<sub>39</sub>00-AAV<sub>1</sub>), kindly share<br>279 from Addgene. Mice were anesthetized using isoflurane and bilaterally injected using a pulled glass pipette in the<br>277 hippocampal DG field (AP: -3.39, ML: ±2.50, DV: -3.4, -2.9, -2.4) with 1 µl pAAV-mDlx-GFP-Fishell-1<br>278 (83900-AAV1), (83900-AAV1), kindly shared by Dr. Gordon Fishell (Dimidschstein, Chen et al. 2016) and purchased<br>from Addgene.<br>Statistical Analysis 282 Bata analysis throughout the study was done blind to the experimental condition when possible. 280<br>281 <u>Statistical Analy</u><br>282 Data analysis th<br>283 Results shown r 281 282 Data analysis throu<br>282 Data analysis throu<br>283 Results shown repre<br>284 samples, and the st<br>285 performed using Gr 283 Results shown represent the mean ± SEM. The number of independent experiments or biological<br>284 samples, and the statistical test employed, are indicated in every case. Statistical analyses were<br>285 performed using Gra samples, and the statistical test employed, are indicated in every case. Statistical analyses were 285 samples, and the statistical test employed, are indicated in every case. Statistical analyses were<br>285 september of the statistical analyses were analysed. Statistical analyses were were analyzed in the statistical ana 285 performancing Graph Catholics y and SutterPatch software.<br>Prism 9 and SutterPatch software.<br>Prism 9 and SutterPatch software.

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## 287 Results<br>288 Truncation of the GluA1 CTD affects AMPAR levels and subcellular distribution.

289 Truncation of the GluA1 CTD in AMPAR<br>290 Truncation of the GluA1 CTD in AMPAR<br>291 behaviors using ACTD GluA1 mice (Fig. 1A). First, we examined whether GluA1 C<br>292 AMPAR subunit levels. We observed that GluA1 levels we 290 type-specific synaptic transmission and plasticity, cognitive function, novelty processing and other<br>291 behaviors using ΔCTD GluA1 mice (Fig. 1A). First, we examined whether GluA1 CTD truncation affect<br>292 AMPAR subu type-specific synaptic transmission and plasticity, cognitive function, novelty processing and other<br>291 behaviors using ΔCTD GluA1 mice (Fig. 1A). First, we examined whether GluA1 CTD truncation affects<br>292 AMPAR subunit 295 GluA1 expression or stability, but does not alter GluA1's synaptic content. In contrast, GluA2 levels were 292 AMPAR subunit levels. We contribute the subsetious of the CTD state of the SPA of the GTD reduced that the loss of the CTD reduced that the loss of the 294 synaptosome-enriched fractions (Fig. 1B, C). These findings suggest that the loss of the CT<br>295 GluA1 expression or stability, but does not alter GluA1's synaptic content. In contrast, GluA<br>296 strongly upregulated in 295 GluA1 expression or stability, but does not alter GluA1's synaptic content. In contrast, GluA2 levels we<br>296 strongly upregulated in  $\triangle CTD$  GluA1 samples, both globally and in the synaptic fraction (Fig. 1B, D).<br>297 Gl 296 Strongly upregulated in  $\triangle CTD$  GluA1 samples, both globally and in the synaptic fraction (Fig. 1B, D).<br>297 GluA<sub>3</sub> levels were unaffected (Fig. 1B, E). Finally, we observed a modest, statistically significant<br>298 incre 296 strongly upregulated in ∆CTD GluA1 samples, both globally and in the synaptic fraction (Fig. 1B, D).<br>297 GluA<sub>3</sub> levels were unaffected (Fig. 1B, E). Finally, we observed a modest, statistically significant<br>298 incre

298 Final and Eucky Hammer (Fig. 22) 298 Finally, we observe a modest, statistically significant<br>299 Finally, we then examined whether GluA1 CTD truncation affects subcellular AMPAR localizatic<br>201 Finally sing an antibod 299 increase in GluA4 levels in 2012 1999<br>200 increase in GluA4 CTD truncation affects subcellular AM<br>201 Using an antibody against the GluA1 ATD, which detects both WT and ΔCTD trun<br>202 observed that, as expected, GluA1 300 Using an antibody against the GluA1 ATD, which detects both WT and ∆CTD truncated GluA1, we<br>302 observed that, as expected, GluA1 immunoreactivity (i.r.) was largely absent from the somata-enriched<br>303 strata pyramidale (S 302 observed that, as expected, GluA1 immunoreactivity (i.r.) was largely absent from the somata-enri<br>303 strata pyramidale (SP) in hippocampal fields CA1-CA3 and granulare (SG) in DG in WT samples.<br>304 Meanwhile, the su 303 strata pyramidale (SP) in hippocampal fields CA1-CA3 and granulare (SG) in DG in WT samples.<br>304 Meanwhile, the subcellular distribution of ΔCTD GluA1 was more diffuse, suggesting impaired<br>305 intracellular traffickin Strata Pyramian (SP) in hipper sample is the SD strate (CP) in Detail (Particular Pietra)<br>304 Meanwhile, the subcellular distribution of ΔCTD GluA1 was more diffuse, suggesting impaired<br>305 The intracellular trafficking ( 305 Meanwhile, the subcellular trafficking (Fig. 1G). Quantification of the soma/dendrite GluA1 ir ratio in CA1 and<br>306 mevealed a significant accumulation of ΔCTD GluA1 in the soma in both regions (Fig. 1H, I), sugge<br>30 305 intracellular trafficking (Fig. 1G). Quantification of the soma/dendrite GluA1 ir ratio in CA1 and DG<br>306 revealed a significant accumulation of ΔCTD GluA1 in the soma in both regions (Fig. 1H, I), suggesting<br>307 that 307 that GluA1 CTD truncation impairs AMPAR soma→dendrite trafficking in CA1 PNs and DG GCs.<br>308 Interestingly, GluA2 subunits showed a similar redistribution in CA1 (Fig. 1J, K), reminiscent of the<br>309 pattern found in G Interestingly, GluA2 subunits showed a similar redistribution in CA1 (Fig. 1J, K), reminiscent of the<br>309 pattern found in GluA1 KOs (Zamanillo D.; Sprengel and Kaiser 1999). GluA2 distribution was not<br>310 significantly al 309 Interestingly, GluA2 subulation in the a similar realistic suburb. The (Fig. 2) A), reminiscent of the<br>310 Interestingly altered in DG (Fig. 1J, L). We then turned to confocal microscopy to further analyze G<br>311 Intere 310 significantly altered in DG (Fig. 1J, L). We then turned to confocal microscopy to further analyze G<br>311 and GluA2 distribution in field CA1 SR and in DG SM, where most excitatory synapses onto CA1 Pl<br>312 and DG GCs, r 311 and GluA2 distribution in field CA1 SR and in DG SM, where most excitatory synapses onto CA1 PNs<br>312 and DG GCs, respectively, occur. Consistent with our previous observations, we found a significant<br>313 decrease in th 312 and DG GCs, respectively, occur. Consistent with our previous observations, we found a significant<br>313 decrease in the density of putative synaptic GluA1 puncta in both CA1 SR and DG SM (Suppl. Fig. 1A,<br>314 The density 313 decrease in the density of putative synaptic GluA1 puncta in both CA1 SR and DG SM (Suppl. Fig. 1/<br>314 The density of the excitatory postsynaptic marker PSD-95 puncta was slightly reduced in CA1 SR (Suppl. Fig. 18), b 314 The density of the excitatory postsynaptic marker PSD-95 puncta was slightly reduced in CA1 SR (Suppl.<br>315 Fig. 1B), but not significantly altered in DG SM (Suppl. Fig. 1D). Despite the significant redistribution of<br>3 315 Fig. 1B), but not significantly altered in DG SM (Suppl. Fig. 1D). Despite the significant redistribution of<br>316 GluA1, its colocalization with PSD-95 was unaffected in both regions in ΔCTD GluA1 samples (Fig. 1M,<br>317 316 GluA1, its colocalization with PSD-95 was unaffected in both regions in  $\triangle CTD$  GluA1 samples (Fig. 1M, N), suggesting that  $\triangle CTD$  GluA1 localization at synapses was not significantly affected. In hippocampal 317 GluAnnia GluAnnia with PSD-95 was unaffected in a synapses was not significantly affected. In hippocampartic in a synapses was unaffected in hippocampartic in  $\frac{1}{2}$  or  $\frac{1}{2}$  M, suggesting that ∆CTD GluA1 local 317 N), suggesting that ∆CTD GluAn localization at symphone was not symmetry affected. In hippocampal<br>In hippocampal localization at significant localization affected. In higher was not significantly affected. In

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- 319 Shi et al. 2009). To reveal possible compensatory changes in AMPAR subunit composition in ΔCTD<br>320 GluA1 mice, we assessed the distribution of GluA2 and GluA3. Putative synaptic puncta densities were<br>321 not altered i 320 GluA1 mice, we assessed the distribution of GluA2 and GluA3. Putative synaptic puncta densities we not altered in CA1 SR or DG SM (Suppl. Fig. 1E-H), and neither was their colocalization (Fig. 1O, P).<br>322 Altogether, 321 out altered in CA1 SR or DG SM (Suppl. Fig. 1E-H), and neither was their colocalization (Fig. 10, P).<br>322 Altogether, these findings indicate that loss of the GluA1 CTD affects intracellular trafficking, but that<br>323 t 222 Altogether, these findings indicate that loss of the GluA1 CTD affects intracellular trafficking, but the<br>323 the synaptic AMPAR complement is largely intact (Fig. 1Q).<br>324 <u>ACTD GluA1 mice exhibit novelty-induced hype</u>
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323 the synaptic AMPAR complement is largely intact (Fig. 1Q).<br>324 Altongether, the GluA1 Complement is largely intact (Fig. 1Q).<br>325 Altong EluA1 Microsofts intracellular trafficking, but that consisted that the impact of 324<br>325 ACTD GluA1 mice exhibit novelty-induced hyperlocomotion<br>326 Having established the impact of GluA1 CTD truncat<br>327 distribution, we sought to clarify whether GluA1-dependent 326 *Alexandron Martin Limited Mindon CTD truncation in AMPAR levels and subcalistribution, we sought to clarify whether GluA1 dependent regulation of cognitive function.<br>323 behavior require the CTD. Previous studies have* 327 distribution, we sought to clarify whether GluA1-dependent regulation of cognitive function and<br>328 behavior require the CTD. Previous studies have shown that GluA1 KO mice have impaired spatia<br>329 working memory, but distribution, we sought to clarify whether GluA1-dependent regulation of cognitive function and<br>328 behavior require the CTD. Previous studies have shown that GluA1 KO mice have impaired spatial<br>329 working memory, but int 329 behavior require the CTD. Previous materials have studied the CMS of Sanderson, Good et al. 2009).<br>330 Novelty-induced hyperlocomotion is one of the most robust and reproducible phenotypes in GluA:<br>331 mice (Zamanillo Sa Sa Sa Novelty-induced hyperlocomotion is one of the most robust and reproducible phenotypes in GluA<br>331 mice (Zamanillo D.; Sprengel and Kaiser 1999, Bannerman, Deacon et al. 2004, Procaccini, Aitta-a<br>332 al. 2011). To mice (Zamanillo D.; Sprengel and Kaiser 1999, Bannerman, Deacon et al. 2004, Procaccini, Aitta-aho et al. 2011). To assess the contribution of the GluA1 CTD to spatial novelty processing, we quantified<br>333 locomotion in t 334 homozygous ACTD GluA1 mice, and observed a strong exacerbation of novelty-induced locomotion in<br>335 ACTD GluA1 mice compared to WTs (Fig. 2A). The center/total distance ratio was similar in WT and locomotion in the open field (OF) test in WT and ΔCTD GluA1 mice. Initially we tested male WT and<br>334 homozygous ΔCTD GluA1 mice, and observed a strong exacerbation of novelty-induced locomotion in<br>335 ΔCTD GluA1 mice com locomotion in the open field (OF) such the and 2012 Declementation of novelty-induced locomotion<br>335 ΔCTD GluA1 mice compared to WTs (Fig. 2A). The center/total distance ratio was similar in WT and<br>336 ΔCTD GluA1 mice (S 335 ΔCTD GluA1 mice compared to WTs (Fig. 2A). The center/total distance ratio was similar in WT and<br>336 ΔCTD GluA1 mice (Suppl. Fig. 2A). ΔCTD GluA1 mice made significantly fewer fine movements (Suppl.<br>337 Fig. 2B) and a ΔCTD GluA1 mice (Suppl. Fig. 2A). ΔCTD GluA1 mice made significantly fewer fine movements (Sup<br>337 Fig. 2B) and a similar number of rearings (Suppl. Fig. 2C) compared to their WT counterparts. In a<br>338 different cohort, Δ 337 ∂Fig. 2B) and a similar number of rearings (Suppl. Fig. 2C) compared to their WT counterparts. In a<br>338 ∂different cohort, ΔCTD GluA1 male and female mice showed indistinguishable exacerbated novelty-<br>339 induced hype Fig. 2B) and a similar number of rearings (Suppl. Fig. 2C) compared to their WT counterparts. In a<br>338 different cohort, ΔCTD GluA1 male and female mice showed indistinguishable exacerbated novelty-<br>339 induced hyperlocom

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338 different cohort, ∆CTD GluA1 male and female mice showed indistinguishable exacerbated novelty-340<br>341 Mext, we assessed the role of the GluA1 CTD in cognitive function. We prevident<br>342 Interval absent in the forced alternation of the fig. 2D), which is used to assess spatial words<br>343 2020). In the forced alternat 342 that GluA1 CTD truncation does not affect spatial reference memory (Diaz-Alonso, Morishita et al.<br>343 zo20). In the forced alternation Y-maze (Fig. 2B), which is used to assess spatial working memory in<br>344 mice, WT a 343 sozo). In the forced alternation Y-maze (Fig. 2B), which is used to assess spatial working memory in mice, WT and ΔCTD GluA1 male and female mice performed comparably (Fig. 2C). Then, we tested<br>345 long-term spatial m 344 mice, WT and ΔCTD GluA1 male and female mice performed comparably (Fig. 2C). Then, we tested<br>345 long-term spatial memory in the object location memory task (OLM, Fig. 2F). As expected from the<br>346 results, we observe 345 Iong-term spatial memory in the object location memory task (OLM, Fig. 2F). As expected from the<br>346 Iong-term spatial memory in the object location memory task (OLM, Fig. 2F). As expected from the<br>347 to the OLM aren 1999 Long-term spatial memory in the organization memory introduced in the organization memory results, we observed enhanced locomotion in ΔCTD GluA1 male and female mice in their first exposure<br>347 to the OLM arena. To a 347 to the OLM arena. To avoid its potential confounding effect, we habituated mice to the OLM arena.<br>348 After 4 days, hyperlocomotion was no longer observed, indicating that ΔCTD GluA1 mice were<br>349 habituated (Fig. 2D 348 After 4 days, hyperlocomotion was no longer observed, indicating that  $\triangle CTD$  GluA1 mice were<br>349 habituated (Fig. 2D, E). Still, total locomotion during OLM training and test were significantly differe 349 habituated (Fig. 2D, E). Still, total locomotion during OLM training and test were significantly d<br>349 habituated (Fig. 2D, E). Still, total locomotion during OLM training and test were significantly d

and the still, the still, total locomotion during OLM training old training and test were significantly different<br>In the still different control to the significant local local local local local local local local local loca

351 Consistent with this possibility, object exploration was also significantly greater in ΔCTD GluA1 mice<br>352 during training and test (Suppl. Fig. 2G, H). Interestingly, ΔCTD GluA1 male and female mice showed<br>353 superi 352 during training and test (Suppl. Fig. 2G, H). Interestingly, ΔCTD GluA1 male and female mice showed<br>353 superior discrimination of the displaced object compared to WT mice (Fig. 2G). We explored whether<br>354 increased 353 superior discrimination of the displaced object compared to WT mice (Fig. 2G). We explored whether<br>354 increased object exploration in ΔCTD GluA1 mice underlies their superior performance, but we found<br>355 o correlat 354 increased object exploration in  $\triangle CTD$  GluA1 mice underlies their superior performance, but we found<br>355 o correlation between distance travelled or object exploration time and performance in the OLM tes<br>356 (Suppl. Fi 355 increased of the distance travelled or object exploration time and performance in the OLM tes<br>356 (Suppl. Fig. 2M, N). In the novel objection recognition task (NOR, Fig. 2H), novel object discriminatior<br>357 was compar 356 (Suppl. Fig. 2M, N). In the novel objection recognition task (NOR, Fig. 2H), novel object discrimination<br>357 was comparable between male and female ΔCTD GluA1 and WT counterparts (Fig. 2I). Neither total<br>358 locomotio 357 (Supplemage and provide on the novel of guide and female  $\triangle CTD$  GluA1 and WT counterparts (Fig. 2I). Neither total<br>358 locomotion nor total object exploration during NOR training and test were significantly different<br>3 937 was comparable between male and female ∆CTD GluA1 and WT counterparts (Fig. 2I). Neither to<br>358 locomotion nor total object exploration during NOR training and test were significantly different<br>359 between genotypes

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362 Contextual fear conditioning and memory are impaired in GluA1 KO mice (Humeau, Reisel et al. 359 between genotypes (Suppl. Fig. 2J-L). 362 Contextual fear conditioning and mem<br>363 2007). Similarly, ΔCTD GluA1 mice did not exhi<br>364 2K, L). Decreased freezing was unlikely due to<br>365 showed enhanced responsiveness in the hot pl 2007). Similarly, ΔCTD GluA1 mice did not exhibit freezing behavior during the conditioning phase (Fig.<br>364 zK, L). Decreased freezing was unlikely due to impaired sensory processing in ΔCTD GluA1 mice, which<br>365 showed e 364 2K, L). Decreased freezing was unlikely due to impaired sensory processing in ΔCTD GluA1 mice, which<br>365 showed enhanced responsiveness in the hot plate test (Suppl. Fig. 2O) and higher motion indices in<br>366 response 365 showed enhanced responsiveness in the hot plate test (Suppl. Fig. 2O) and higher motion indices in<br>366 response to the two initial foot shocks (0.45 mA) delivered during conditioning (Suppl. Fig. 2P).<br>367 Unexpectedl 1366 response to the two initial foot shocks (0.45 mA) delivered during conditioning (Suppl. Fig. 2P).<br>367 Unexpectedly, ΔCTD GluA1 mice showed freezing comparable to WTs in the 24 h recall test (Fig. 2N)<br>368 in stark con 367 Unexpectedly, ΔCTD GluA1 mice showed freezing comparable to WTs in the 24 h recall test (Fig. in stark contrast to GluA1 KOs, which show impaired fear expression and memory (Humeau, Re<br>369 zoo7). In both WT and ΔCTD G 368 in stark contrast to GluA1 KOs, which show impaired fear expression and memory (Humeau, Reisel et al.<br>369 2007). In both WT and ΔCTD GluA1 animals, the % freezing during conditioning was not predictive of<br>370 freezing 369 in stand contrast to GluA1 Animals, the % freezing during conditioning was not predictive of<br>370 freezing during the 24 h recall test (Suppl. Fig. 2Q). These findings support that GluA1-dependent<br>371 contextual memory 370 freezing during the 24 h recall test (Suppl. Fig. 2Q). These findings support that GluA1 dependent<br>371 contextual memory formation does not require the CTD. Fear generalization was not affected either,<br>372 supporting 371 contextual memory formation does not require the CTD. Fear generalization was not affected eith<br>372 supporting that context discrimination and memory function is intact in ΔCTD GluA1 mice (Suppl.<br>373 2R, S).<br>374 372 supporting that context discrimination and memory function is intact in ΔCTD GluA1 mice (Suppl. Fig<br>373 2R, S).<br>374 Next, we sought to identify the mechanism underlying the apparent discrepancy between

supporting that context discrimination and memory function is intact in ∆CTD GluA1 mice (Suppl.<br>373 zR, S).<br>374 Next, we sought to identify the mechanism underlying the apparent discrepancy between<br>376 impaired contextua --- ---<sub>---</sub>--,<br>374<br>375 impaire<br>377 hypoth 374 376 Impaired contextual fear expression (Fig. 2K, L) and intact contextual memory (Fig. 2M, N). We<br>377 Impothesized that the exacerbated context novelty-driven hyperlocomotion in ΔCTD GluA1 mice<br>378 Imasks freezing during 377 hypothesized that the exacerbated context novelty-driven hyperlocomotion in ΔCTD GluA1 middle masks freezing during conditioning, although it does not affect contextual memory formation.<br>379 prediction were true, we w 378 masks freezing during conditioning, although it does not affect contextual memory formation. If t<br>379 prediction were true, we would expect that reducing context novelty (hence decreasing<br>380 hyperlocomotion) would un 379 prediction were true, we would expect that reducing context novelty (hence decreasing<br>380 hyperlocomotion) would unmask freezing during fear conditioning. We tested this by assessing<br>381 contextual fear expression afte 380 hyperlocomotion) would unmask freezing during fear conditioning. We tested this by as<br>381 contextual fear expression after a 30-min. context pre-exposure session 24 h prior to context<br>381 contextual fear expression aft 381 contextual fear expression after a 30-min. context pre-exposure session 24 h prior to conditioning.<br>381 contextual fear expression after a 30-min. context pre-exposure session 24 h prior to conditioning. 381 contextual fear expression after a 30-min. context pre-exposure session 24 h prior to conditioning (Fig.

382 3A). Context pre-exposure did not affect freezing during conditioning or contextual memory in WT mice<br>383 (Fig. 3B, E) but, as predicted, partially normalized freezing in  $\triangle CTD$  GluA1 mice (Fig. 3B, C). As expected<br>38 384 from previous findings (Fig. 2M, N), performance at the 24-hour recall test was indistinguishable from<br>385 that of WT mice (Fig. 3D, E). Shock response was indistinguishable between ΔCTD GluA1 and WT mice<br>386 in this 385 that of WT mice (Fig. 3D, E). Shock response was indistinguishable between ΔCTD GluA1 and WT mice<br>386 in this cohort (Suppl. Fig. 3). These findings support the notion that the GluA1 CTD plays a critical<br>387 regulator 386 in this cohort (Suppl. Fig. 3). These findings support the notion that the GluA1 CTD plays a critical<br>387 that of WT microscopy of WT microscopy was indicated between  $\frac{1}{2}$  and  $\frac{1}{2}$  and  $\frac{1}{2}$  and  $\frac{1}{2}$ 1987 in this control (Supple 1936). These finally support the notion that the GluA<sub>1</sub> conduction that the plays a<br>388 in the notion of the notion of the set of GluA1 CHD plays a critical schizoaffective disorder-related be

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388<br>389 Additional schizoaffective disorder-related behavioral alterations evoked by GluA1 CTD<br>390 Next, we studied whether GluA1 CTD truncation alone is sufficient to elicit other<br>391 alterations relevant to schizoaffecti 390 Next, we studied whether GluA1 CTD truncation alone is sufficient to elicit other behavioral<br>391 alterations relevant to schizoaffective disorders. In the elevated plus maze (EPM, Fig. 4A), ΔCTD Glu<br>392 male mice spen 391 alterations relevant to schizoaffective disorders. In the elevated plus maze (EPM, Fig. 4A), ΔCTD Glu<br>392 male mice spent a greater proportion of the time exploring the open arms (Fig. 4B) throughout the<br>393 session ( 392 alterations relevant to sumstain the explorement to schick processes (Fig. 4B) throughout the<br>393 alternations relevant of the time exploring the open arms (Fig. 4B) throughout the<br>394 alternations relevant of the tim 393 session (Suppl. Fig. 4A). Consistently, the number of open arm entries (Fig. 4C) and distance (Suppl<br>394 4B), but not closed arm entries (Fig. 4D) and distance (Suppl. Fig. 4C) were increased in male ΔCTD<br>395 GluA1 mi 393 session (Suppl. Fig. 4A). Consistently, the number of open arm entries (Fig. 4C) and distance (Suppl. Fig. 395 GluA1 mice. Consistent with previous results (Fig. 2A, Suppl. Fig. 2D), ΔCTD GluA1 mice displayed a<br>396 overall increase in total distance traveled in the EPM relative to their WT counterparts (Suppl. Fig. 4<br>397 The GluA1 mice. Consistent with previous results (Fig. 2A, Suppl. Fig. 2D), ΔCTD GluA1 mice displayed an<br>396 overall increase in total distance traveled in the EPM relative to their WT counterparts (Suppl. Fig. 4D).<br>397 The 399 explore the apparently reduced anxiety in  $\Delta$ CTD GluA1 mice, we applied the light/dark transition test,<br>400 which can also reveal changes in anxiety-like behavior (Fig. 4E). Latency to enter the dark (safe) zone 398 the GluA1 KO mice phenotype (Fitzgerald, Barkus et al. 2010), albeit perhaps exacerbated. To further explore the apparently reduced anxiety in ΔCTD GluA1 mice, we applied the light/dark transition test, which can als 399 explore the apparently reduced anxiety in ΔCTD GluA1 mice, we applied the light/dark transition test,<br>300 which can also reveal changes in anxiety-like behavior (Fig. 4E). Latency to enter the dark (safe) zone<br>301 was 399 explore the appearancy reduced annually reduced and set in 2000 (Fig. 4E). Latency to enter the dark (safe) zone<br>399 which can also reveal changes in anxiety-like behavior (Fig. 4E). Latency to enter the dark (safe) z which carrelate reveal changes in annually line behavior (Fig. 4F). The total time spent in each zone was n<br>402 altered (Suppl. Fig. 4E). Additionally, in the forced swim test (FST, Fig. 4G), used to measure despair-<br>403 was increased in ∆CTD GluA1 male and female mice (Fig. 4F). The total time spent in each zone was r<br>402 altered (Suppl. Fig. 4E). Additionally, in the forced swim test (FST, Fig. 4G), used to measure despair-<br>403 like be like behavior in rodents, we found that  $\Delta$ CTD GluA1 male and female mice spent less time immobile<br>404 compared to their WT counterparts (Fig. 4H). Latency to immobility was not significantly affected<br>405 (Suppl. Fig. 4F compared to their WT counterparts (Fig. 4H). Latency to immobility was not significantly affected<br>405 (Suppl. Fig. 4F). These findings indicate that the CTD is required for GluA1-dependent novelty<br>406 processing and regul 405 (Suppl. Fig. 4F). These findings indicate that the CTD is required for GluA1-dependent novelty<br>406 processing and regulates risk assessment, approach behavior and/or anxiety. Conversely, our c<br>407 indicates that the CT Fig. 19 processing and regulates risk assessment, approach behavior and/or anxiety. Conversely, our c<br>105 indicates that the CTD is not required for GluA1-dependent memory processes.<br>108 Exacerbated neuronal activity in th 407 indicates that the CTD is not required for GluA1-dependent memory processes.<br>408 Exacerbated neuronal activity in the DG in  $\triangle$ CTD GluA1 mice following exposure to a novel<br>410 Environment. 408<br>409 Exacerbated neuronal activity in the DG in ACTD GluA1 mice following exposure<br>410 environment.<br>411 To identify the neurobiological mechanism underlying the regulation of 408

environment.<br>410 Environment.<br>411 To identify the neurobiological mechanism underlying the regulation of novelty pro<br>412 the GluA1 CTD, we sought to identify neuronal populations which respond to novelty in a G<br>413 depende 411 To ide<br>412 the GluA1 CTD<br>413 dependent fas 112 the GluA1 CTD, we sought to identify neuronal populations which respond to novelty in a GluA1 CTD-<br>413 dependent fashion. To this end, we quantified c-Fos expression, a proxy for neuronal activation, two<br>413 dependent 413 dependent fashion. To this end, we quantified c-Fos expression, a proxy for neuronal activation, two<br>413 dependent fashion. To this end, we quantified c-Fos expression, a proxy for neuronal activation, two<br>413 dependen

 $\mathcal{A}_1$  dependent fashion. To this end, we quantified co-Fos expression, a proxy for neuronal activation, two  $\mathcal{A}_2$ 

414 hours after exposure to a novel environment (Fig. 5A). Increased c-Fos-labelled cells were observed in<br>415 various brain regions in WT male and female mice upon exposure to a novel context (Fig. 5, Suppl. Fig.<br>416 5). 416 5). In dorsal hippocampus, c-Fos induction was exacerbated in putative DG GCs and field CA<sub>3</sub> PNs in<br>417 ΔCTD GluA1 male and female mice compared to WTs after OF exposure (Fig. 5B-D). c-Fos expression<br>418 increased to 417 ΔCTD GluA1 male and female mice compared to WTs after OF exposure (Fig. 5B-D). c-Fos expression<br>418 Increased to a similar degree in WT and ΔCTD GluA1 mice in field CA1 (Fig. 5E). The similarity of thes<br>419 Increased 418 increased to a similar degree in WT and ΔCTD GluA1 mice in field CA1 (Fig. 5E). The similarity of these<br>419 results with those previously reported in GluA1 KO mice (Procaccini, Aitta-aho et al. 2011), suggests<br>420 tha 119 increased to a similar degree in the similar decreasing to a similar degree in GluA1 (Procaccini, Aitta-aho et al. 2011), suggests<br>420 that the CTD is critically required for GluA1-dependent regulation of hippocampal 420 that the CTD is critically required for GluA1-dependent regulation of hippocampal activity upon<br>421 exposure to a novel context.<br>422 The GluA1 CTD regulates excitatory synapses onto dentate gyrus GABAergic interneurons that the CTD is critically required for GluA1-dependent regulation of hippocampal activity upon<br>
421 exposure to a novel context.<br>
422 The GluA1 CTD regulates excitatory synapses onto dentate gyrus GABAergic interneurons.<br>

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423 The GluA1 CTD regulates exc<br>
424 Excessive c-Fos expre<br>
425 synaptic transmission onto the 425 synaptic transmission onto these cells. To test this possibility, we obtained whole-cell patch-clamp<br>426 recordings from DG GCs using acute brain slices form  $\triangle$ CTD GluA1 and WT mice (Fig. 6A) and exam<br>427 excitatory Expressive complements in the suppression of the set of alternative consequence of alternative<br>425 Synaptic transmission onto these cells. To test this possibility, we obtained whole-cell patch-clamp<br>427 excitatory synap erative cordings from DG GCs using acute brain slices form ΔCTD GluA1 and WT mice (Fig. 6A) and examence cells<br>427 excitatory synaptic transmission at perforant path (PP)  $\rightarrow$  GC synapses. We observed no significant<br>428 c excitatory synaptic transmission at perforant path (PP)→GC synapses. We observed no significant<br>428 changes in AMPAR/NMDAR ratios (Fig. 6B), indicating that AMPAR-mediated transmission is not<br>429 severely affected in ΔCT charactery sympths in manufacture performance path (PP) (CD) (Mp) CDC) material in any simulated transmission is not<br>429 exercely affected in  $\Delta CTD$  GluA1 DG GCs. Consistently, input/output AMPAR EPSC analysis showed<br>430 s examples in AMPAR ratios (Fig. 6C), consistently, input/output AMPAR EPSC analysis showe<br>430 significant differences either (Fig. 6C), confirming that AMPAR-mediated synaptic transmission is<br>431 argely intact in these cel 430 significant differences either (Fig. 6C), confirming that AMPAR-mediated synaptic transmission is<br>431 largely intact in these cells. Then, we assessed whether the loss of the GluA1 CTD affects LTP at<br>432 PP→DG GC syn 1431 Iargely intact in these cells. Then, we assessed whether the loss of the GluA1 CTD affects LTP at<br>1432 PP→DG GC synapses. We found a small, non-statistically significant reduction in GCs LTP in ΔCTD<br>1433 GluA1 mice (F 432 PP→DG GC synapses. We found a small, non-statistically significant reduction in GCs LTP in ΔC<br>433 GluA1 mice (Fig. 6D). Altogether, these results suggest that alterations in synaptic transmission<br>434 LTP in DG GCs are 433 GluA1 mice (Fig. 6D). Altogether, these results suggest that alterations in synaptic transmission and<br>434 LTP in DG GCs are unlikely to underlie the exacerbated neuronal activation observed following nove<br>435 context GluA1 mice (Fig. 6D). Altogether, these results suggest that alterations in synaptic transmission and<br>134 LTP in DG GCs are unlikely to underlie the exacerbated neuronal activation observed following novel<br>135 context expo

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1946 LTP in the DD Case are unlikely to underlie the underlient statement activation of the exaction of 435<br>136<br>137 Local INs provide inhibitory inputs to DG GCs, thus regulating their excitability, spike timing,<br>138 and l 1986<br>136 Local INs p<br>137 Local INs p<br>138 and lateral inhibitie<br>139 2016, Pelkey, Chitt and lateral inhibition, and ultimately contributing to the sparse activity of DG GCs (Akgul and McBain<br>139 and lateral inhibition, and ultimately contributing to the sparse activity of DG GCs (Akgul and McBain<br>140 truncati 2016, Pelkey, Chittajallu et al. 2017, Espinoza, Guzman et al. 2018). We hypothesized that GluA1 CTD<br>440 truncation might affect AMPAR-mediated excitatory synaptic transmission onto GABAergic INs in DG<br>441 thereby compromi 440 truncation might affect AMPAR-mediated excitatory synaptic transmission onto GABAergic INs in DG<br>441 thereby compromising circuit inhibition and potentially leading to the observed GCs 'priming'. To<br>442 identify inhib 441 thereby compromising circuit inhibition and potentially leading to the observed GCs 'priming'. To<br>442 identify inhibitory cells, we bilaterally injected an AAV-mDLX-GFP, which labels forebrain GABAergic<br>443 INs, into 1994) identify inhibitory cells, we bilaterally injected an AAV-mDLX-GFP, which labels forebrain GABAe<br>1943 INS, into the DG of WT and ACTD GluA1 littermates. After ~4 weeks of expression, GABAergic cell<br>1944 Were labelled 443 INs, into the DG of WT and ΔCTD GluA1 littermates. After ~4 weeks of expression, GABAergic cells<br>444 were labelled throughout the hippocampus in acute slices (Fig. 6E). We obtained whole-cell recording<br>445 from putati 144 Institute the DDM of WATERO of WATEROM (Fig. 66). We obtained whole-cell recordinate to the proportion of W<br>445 Internative DG parvalbumin (PV)+ basket cells, identified by their morphology and localization of<br>445 Int 444 were labelled throughout the hippocampus in acute slices (Fig. 6E). We obtained whole-cell recordings<br>445 from putative DG parvalbumin (PV)+ basket cells, identified by their morphology and localization of the  $445$  from putative DG particle DG particle  $\binom{1}{k}$  and localization of the interpretation of the their morphology and localization of the interpretation of the interpretation of the interpretation of the interpretatio

446 soma within SG. We found a significant reduction in AMPAR/NMDAR ratios in these cells (Fig. 6F),<br>447 indicating that the loss of the GluA1 CTD affects synaptic transmission in DG GABAergic INs, in contrast<br>448 to the 148 to the intact synaptic transmission observed onto GCs. The specific reduction of excitatory synaptic<br>449 drive onto DG GABAergic cells explains, at least in part, the exacerbated DG responsiveness to novelty<br>450 and su 449 drive onto DG GABAergic cells explains, at least in part, the exacerbated DG responsiveness to nove<br>450 and subsequent behavioral alterations observed in  $\triangle CTD$  GluA1 mice.<br>451 Discussion

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## 452 Discussion<br>453 Glu.

and subsequent behavioral alterations observed in  $\triangle$ CTD GluA1 mice.<br>451 Discussion<br>452 Discussion GluA1-deficient mice exhibit deficits in synaptic plasticity and behavioral alterations, such as 451 and subsequent behavior of the hard subsequent behavior of the lines.<br>452 Discussion<br>453 GluA1-deficient mice exhibit deficits in synaptic plasticity and<br>454 selective deficits in short-term habituation and exacerbate selective deficits in short-term habituation and exacerbated novelty-induced locomotor hyperactivity,<br>455 reminiscent of some of the features of schizoaffective disorders and neurodevelopmental conditions<br>456 including att 457 zo12, Barkus, Sanderson et al. 2014). Consistently, mutations in the *GRIA1* gene, which encodes GLUA1, 458<br>458 may increase risk of schizophrenia in humans (Coyle 2006, Ripke, O'Dushlaine et al. 2013, 1986 including attention-deficit/hyperactivity disorder (Fitzgerald, Barkus et al. 2010, Barkus, Feyder et al.<br>1957 2012, Barkus, Sanderson et al. 2014). Consistently, mutations in the *GRIA1* gene, which encodes GLU<br>1988 2012, Barkus, Sanderson et al. 2014). Consistently, mutations in the *GRIA1* gene, which encodes GLU<br>458 may increase risk of schizophrenia in humans (Coyle 2006, Ripke, O'Dushlaine et al. 2013,<br>5Chizophrenia Working Group 457 2012, Barkus, Sanderson et al. 2014). Consistently, motations in the OMA1 gene, which encodes GLOA1,<br>458 may increase risk of schizophrenia in humans (Coyle 2006, Ripke, O'Dushlaine et al. 2013,<br>5 Schizophrenia Working 458 may increase risk of schizophrenia in humans (Coyle 2006, Ripke, O'Dushlaine et al. 2013,<br>459 Schizophrenia Working Group of the Psychiatric Genomics 2014, Ismail, Zachariassen et a<br>460 Yonezawa, Tani et al. 2022).<br>462

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Schizophrenia Working Group of the Psychiatric Genomics 2014, Ismail, Zachariassen et al. 2022,<br>160 Yonezawa, Tani et al. 2022).<br>161 What makes GluA1 unique among AMPAR subunits? The GluA1 CTD is the most sequence-<br>163 div 461<br>462 What makes GluA1 u<br>463 diverse area of the receptor a<br>464 interest, its role, especially at diverse area of the receptor and has therefore drawn considerable attention for decades. Despite the interest, its role, especially at synapses outside of hippocampal field CA1, is largely unexplored. In the study, we used 1444 interest, its role, especially at synapses outside of hippocampal field CA1, is largely unexplored. In this<br>1465 study, we used constitutive GluA1 CTD-truncated mice to explore crucial aspects of how the CTD<br>1466 affe 1644 interest, its role, especially at synapses outside of impposant particles of layer rangely ontifipersed.<br>1644 interest GluA1's localization and function at the biochemical, cellular and behavioral level. We found this affects GluA1's localization and function at the biochemical, cellular and behavioral level. We four<br>467 the GluA1 CTD regulates AMPAR subunit protein levels, intracellular trafficking and synaptic<br>468 transmission onto in the GluA1 CTD regulates AMPAR subunit protein levels, intracellular trafficking and synaptic<br>468 transmission onto inhibitory, but not excitatory neurons in the DG, ultimately affecting GC excitability<br>469 and spatial nove 1468 transmission onto inhibitory, but not excitatory neurons in the DG, ultimately affecting GC ex<br>1469 and spatial novelty processing. We found no evidence of memory impairments upon loss of t<br>1470 CTD, and in fact we ob and spatial novelty processing. We found no evidence of memory impairments upon loss of the GluA1<br>470 transmission of the Australian CTD, and in fact we observed enhanced performance in OLM. Altered performance in the FST, 470 CTD, and in fact we observed enhanced performance in OLM. Altered performance in the FST, EPM<br>471 and light/dark alternation tests suggest additional regulation of affective processes by the GluA1 CTD.<br>472 In a previou and light/dark alternation tests suggest additional regulation of affective processes by the GluA1 CTI<br>472 In a previous study we did not observe qualitative changes in AMPAR subunit expression in<br>474 ACTD GluA1 mice (Diaz

472 and light, and light alternative tests suggest and light alternative processes procession in<br>474 and a previous study we did not observe qualitative changes in AMPAR subunit expression in<br>474 and CTD GluA1 mice (Diaz-472<br>473 ACTD GluA1 mice (Diaz-Alonso, Morishita et al. 2020). However, more detailed analysis in this studer revealed that GluA1 subunit levels and subcellular distribution are, in fact, affected by the loss of the GluA1 CTD. We 475 revealed that GluA1 subunit levels and subcellular distribution are, in fact, affected by the loss of the<br>476 GluA1 CTD. We also found that the CTD influences intracellular GluA1 trafficking, consistent with<br>477 previ 476 GluA1 CTD. We also found that the CTD influences intracellular GluA1 trafficking, consistent with<br>477 previous reports highlighting the importance of GluA1 CTD interactions with 4.1N and SAP97 in 176 GluAn Chern From the Construction that the Construction of GluA1 CTD interactions with 4.1N and SAP97 in<br>477 previous reports highlighting the importance of GluA1 CTD interactions with 4.1N and SAP97 in  $\frac{1}{2}$  previous reports highlighting the importance of GluAn C $\alpha$ 1  $\beta$ 

478 intracellular AMPAR trafficking (Shen, Liang et al. 2000, Sans, Racca et al. 2001, Bonnet, Charpentier et<br>479 al. 2023). Interestingly, despite reduced GluA1 levels and altered intracellular trafficking, we found that<br> 480 both GluA1's abundance at synaptosomes and its colocalization with PSD-95 were not significantly<br>481 affected by truncation of the CTD. These findings suggest that, despite reduced soma →dendrite<br>482 trafficking, syna 481 affected by truncation of the CTD. These findings suggest that, despite reduced soma→dendrite<br>482 trafficking, synaptic AMPAR docking is not significantly affected by the truncation of the GluA1 CTI<br>483 This is consis 482 trafficking, synaptic AMPAR docking is not significantly affected by the truncation of the GluA1 C<br>483 This is consistent with the normal AMPAergic transmission in ΔCTD GluA1-expressing CA1 PNs<br>484 (Granger, Shi et al 483 This is consistent with the normal AMPAergic transmission in ΔCTD GluA1-expressing CA1 PNs<br>484 (Granger, Shi et al. 2013, Diaz-Alonso, Morishita et al. 2020, Watson, Pinggera et al. 2021) and DG GC<br>485 (present study) 484 This is consistent with the normal and norge transmission in 2012 This inpressing in ∆CTD<br>485 (present study).<br>486 GluA2 protein levels were dramatically increased in ∆CTD GluA1 mice, in stark contrast

Granger, Shi et al. 2013, Diaz-Alonso, Morishita et al. 2020, Watson, Pinggera et al. 2021) and DG GCs<br>
485 (present study).<br>
486 GluA2 protein levels were dramatically increased in ΔCTD GluA1 mice, in stark contrast with 485 (present study). For the protein and a manufacture of the statements of the statements, increased to the some included GluA2 levels reported in GluA1 KO mice (Zamanillo, Sprengel et al. 1999,<br>488 Jensen, Kaiser et al. 2003). Furthermore, Jensen, Kaiser et al. 2003). Furthermore, GluA2, but not GluA3 subunits, also appeared enriched in the soma in ACTD GluA1 mice, suggesting that GluA2 can form stable heteromeric receptors with ACTD GluA1 and that the GluA1 489 soma in ΔCTD GluA1 mice, suggesting that GluA2 can form stable heteromeric receptors with ΔCTD<br>490 GluA1 and that the GluA1 CTD exerts a significant influence in intracellular trafficking of GluA1/A2<br>491 AMPARs. Altog 490 GluA1 and that the GluA1 CTD exerts a significant influence in intracellular trafficking of GluA1/A2<br>491 AMPARs. Altogether, these findings support the notion that the GluA1 subunit, both via its ATD (Dia:<br>492 Alonso, 491 AMPARs. Altogether, these findings support the notion that the GluA1 subunit, both via its ATD (D<br>492 Alonso, Sun et al. 2017) and its CTD (present study), dominate heteromeric AMPAR trafficking.<br>493 Together with the 492 Alonso, Sun et al. 2017) and its CTD (present study), dominate heteromeric AMPAR trafficking.<br>493 Together with the normal levels and localization observed for GluA3, and the unaltered GluA2/A3<br>494 colocalization in Δ 493 Together with the normal levels and localization observed for GluA<sub>3</sub>, and the unaltered GluA<sub>2</sub>/<br>494 colocalization in ΔCTD GluA1 hippocampi, these findings suggest that CTD-lacking GluA1 parta<br>495 synaptic transmiss 493 Together with the normal levels and localization observed for GluA<sub>3</sub>, and the unaltered GluA<sub>2</sub>/A<sub>3</sub><br>494 colocalization in  $\triangle CTD$  GluA<sub>1</sub> hippocampi, these findings suggest that CTD-lacking GluA<sub>1</sub> partakes in<br>495 sy 195 synaptic transmission similarly to WT GluA1, and that the normal synaptic transmission and plasticity<br>196 observed at CA1 PNs and DG GCs are not a result of a replacement of GluA1-containing AMPARs by<br>198 The mechanis observed at CA1 PNs and DG GCs are not a result of a replacement of GluA1-containing AMPARs by<br>497 GluA2/A3 heteromers.<br>The mechanisms regulating AMPAR trafficking and synaptic complement are poorly<br>499 understood outside

499 onderstood outside of hippocampal field CA1, despite the prevalence of AMPAR-mediated synaptic<br>1900 transmission throughout the CNS. Here we found that DG GCs are "primed" in ACTD GluA1 mice, an 498 The mechanism<br>499 understood outside of l<br>500 transmission througho 499 understood outside of hippocampal field CA1, despite the prevalence of AMPAR-mediated synaptians regulated by<br>500 transmission throughout the CNS. Here we found that DG GCs are "primed" in ΔCTD GluA1 n<br>501 become exce 499 transmission throughout the CNS. Here we found that DG GCs are "primed" in ΔCTD GluA1 mice, an<br>501 become excessively active following spatial novelty exposure, presumably contributing to<br>502 hyperlocomotion. A recent 501 become excessively active following spatial novelty exposure, presumably contributing to<br>502 hyperlocomotion. A recent study offered a plausible explanation for GC overactivity in ΔCTD GluA1<br>503 mice, showing that AM become excessively active transming spatial novelty exposes; presumate, strateging or<br>502 by hyperlocomotion. A recent study offered a plausible explanation for GC overactivity in ΔCT<br>504 escapes SAP97-mediated retention 503 mice, showing that AMPAR EPSCs are enhanced in GCs overexpressing CTD-lacking GluA1, which<br>504 escapes SAP97-mediated retention at perisynaptic sites (Kay, Tsan et al. 2022). In this study, we did<br>505 find increased 504 escapes SAP97-mediated retention at perisynaptic sites (Kay, Tsan et al. 2022). In this study, we di<br>505 find increased AMPAR EPSCs in ACTD GluA1 mice, possibly because of the different approach<br>506 (constitutive GluA1 505 find increased AMPAR EPSCs in ΔCTD GluA1 mice, possibly because of the different approach<br>506 (constitutive GluA1 CTD truncation *vs* acute overexpression of CTD-truncated GluA1) or species (mouse<br>507 vs rat) employed 506 finance and the Dampart of the Diverent Ample Press, a series of the amplitude (Constitutive GluA1 CTD truncation vs acute overexpression of CTD-truncated GluA1) or specie<br>507 strat) employed in the two studies. Inst 507 vs rat) employed in the two studies. Instead, we found an alternative possibility: AMPAR EPSCs on DG<br>508 inhibitory INs are significantly smaller in ACTD GluA1 mice, which conceivably leads to decreased<br>508 inhibitory 507 strat) employed in the two studies. Instead, we found an alternative possibility. AMPAR EPSCs on DG<br>508 inhibitory INs are significantly smaller in  $\Delta$ CTD GluA1 mice, which conceivably leads to decreased  $\frac{1}{\sqrt{2}}$  inhibitory INS are significantly smaller in  $\frac{1}{\sqrt{2}}$  conceivably leads to decrease

509 inhibition onto DG GCs and may thereby render DG GCs prone to overactivation by excitatory inputs,<br>510 especially those conveying novelty. These findings are consistent with a previous report showing that<br>511 chemogen 511 chemogenetic hippocampal inhibition normalized novelty-induced locomotion in GluA1 KO mice<br>512 (Aitta-Aho, Maksimovic et al. 2019). Our results suggest that, while altered AMPAR subunit levels and<br>513 intracellular tra 512 (Aitta-Aho, Maksimovic et al. 2019). Our results suggest that, while altered AMPAR subunit levels<br>513 intracellular trafficking affect various neuron types in ΔCTD GluA1 mice, certain AMPAR subunit<br>514 compositions, s Fig. 2012 (Materian, Maksimovic et al. 2019). Our results engages that, while altered AMPAR subunit<br>513 Intracellular trafficking affect various neuron types in ΔCTD GluA1 mice, certain AMPAR subunit<br>515 Intractularly sen 514 compositions, such as the GluA1/GluA4 heteromers that dominate in fast-spiking PV+ INs, are<br>515 particularly sensitive to the truncation of the GluA1 CTD. Meanwhile, excitatory neurons may mo<br>516 easily compensate the 515 particularly sensitive to the truncation of the GluA1 CTD. Meanwhile, excitatory neurons may r<br>516 easily compensate the truncation of the GluA1 CTD. The increased levels of GluA<sub>4</sub>, whose expr<br>517 essentially restric Faraction, Tenderston, Tenderston in the truncation of the GluA1 CTD. The increased levels of GluA<sub>4</sub>, whose expressio<br>517 essentially restricted in the forebrain to PV+INs, is additional support for their specific vulner easily compensate the truncation of the GluA1 CTD. The increased levels of GluA4, whose expression i<br>517 essentially restricted in the forebrain to PV+INs, is additional support for their specific vulnerability in<br>518 the

PV+ INs dysfunction can contribute to the pathophysiology of schizophrenia (Lisman, Coyle et 519 the ⊿CTD GluAnd GluAnnian Dypensatory Mechanism involving the 2nd<br>520 the DV+ INs dysfunction can contribute to the pathophysiology of schizophrenia (Lisman,<br>522 al. 2008, Curley and Lewis 2012, Marin 2012, Ruden, Dug 520<br>521 pv+<br>522 al. 2008, Cul<br>523 INs can sign 521 522 al. 2008, Curley and Lewis 2012, Marin 2012, Ruden, Dugan et al. 2021). Altered AMPAR function in PV<br>523 INs can significantly affect their output and function, as exemplified in PV+ IN-specific GluA1 KO mice,<br>524 whic 523 INs can significantly affect their output and function, as exemplified in PV+ IN-specific GluA1 KO mice,<br>524 which show impaired short-term habituation (Fuchs, Zivkovic et al. 2007), and excitation/inhibition<br>525 imbal 524 INSEE INSTRIMENT TREFERTMENT AND THE INTERPTION INTERPTION INTERPTION (STATE THEOD)<br>525 Inbalance reminiscent of that found in patients with schizophrenia (Chen-Engerer, Jaeger et al. 2022).<br>526 Other manipulations suc 525 imbalance reminiscent of that found in patients with schizophrenia (Chen-Engerer, Jaeger et al. 2023).<br>526 Other manipulations such as the deletion of Erbb4 in PV+INs, which lead to a reduction in AMPAR<br>527 content in 526 Other manipulations such as the deletion of Erbb4 in PV+ INs, which lead to a reduction in AMPAR<br>527 content in excitatory synapses onto PV+INs, also result in schizophrenia-related phenotypes (Del Pino,<br>528 Garcia-Fri 527 Content in excitatory synapses onto PV+INs, also result in schizophrenia-related phenotypes (Del P<br>528 Garcia-Frigola et al. 2013). The important role of the GluA1 CTD supporting excitatory synapses on<br>529 putative PV+ 528 Garcia-Frigola et al. 2013). The important role of the GluA1 CTD supporting excitatory synapses onto<br>529 putative PV+INs unveiled in this study expands our understanding of the mechanisms underlying cell<br>530 type-speci 529 putative PV + INs unveiled in this study expands our understanding of the mechanisms underlying cell<br>530 type-specific AMPAR transmission, disruptions of which potentially contribute to altered synaptic<br>531 transmissio 129 putative Protection in the mechanism and the mechanism of which potentially contribute to altered synaptic<br>132 transmission in schizoaffective disorders.<br>133 Our study discriminates between CTD-dependent and independen

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531 transmission in schizoaffective disorders.<br>532 Our study discriminates between CTD-dependent and independent GluA1 cognitive proce<br>534 on one hand, we demonstrate that spatial working memory, object recognition memory 532 transmission in suitable transmission<br>533 tour study discriminates between<br>534 on one hand, we demonstrate that spatial<br>535 contextual fear memory – all of which are on one hand, we demonstrate that spatial working memory, object recognition memory and long-term<br>535 contextual fear memory – all of which are impaired in GluA1 KO mice (Reisel, Bannerman et al. 2002,<br>536 Humeau, Reisel et 535 contextual fear memory – all of which are impaired in GluA1 KO mice (Reisel, Bannerman et al. 2002,<br>536 Humeau, Reisel et al. 2007, Sanderson, Good et al. 2009), are not affected by the loss of the GluA1 CTD.<br>537 Remar 536 Humeau, Reisel et al. 2007, Sanderson, Good et al. 2009), are not affected by the loss of the GluA1 CT<br>537 Remarkably, OLM is enabled after subthreshold training. On the other hand, we find that GluA1 CTD<br>538 truncatio For a constraint served by the loss of the loss of the other hand, we find that GluA1 CTD<br>538 Funcation alone is sufficient to reproduce aberrant salience, short-term habituation and general<br>539 Funcation alone is suffici For a contention of the subtracture of the other handing. On the other hand, ho that GluAn training to the other<br>538 truncation alone is sufficient to reproduce aberrant salience, short-term habituation and general<br>539 co The context of the interaction alone is sufficient to represent the context of term habituation and general res<br>539 tresponse to novelty. The normalization of fear expression during contextual fear conditioning by<br>540 cont 540 context pre-exposure suggests that disrupted fear response in  $\triangle$ CTD GluA1 mice is secondary to a context pre-exposure suggests that disrupted fear response in  $\triangle$ CTD GluA1 mice is secondary to a context pre-exposure

 $540$  context pre-exposure suggests that disputed fear response in  $\alpha$  response in  $\alpha$  microscopic in  $\alpha$ 

542 novelty processing necessitates the CTD.<br>543 GluA1 KO mice are considered a valuable tool to study altered synaptic function in<br>545 Schizophrenia (Fitzgerald, Barkus et al. 2010, Barkus, Feyder et al. 2012, Bygrave, Ja 543<br>544 GluA1 KO mice are considered a v<br>545 schizophrenia (Fitzgerald, Barkus et al. 20<br>546 2019). Here we found that GluA1 CTD trur 543 545 schizophrenia (Fitzgerald, Barkus et al. 2010, Barkus, Feyder et al. 2012, Bygrave, Jahans-P<br>546 zo19). Here we found that GluA1 CTD truncation alone recapitulated the schizoaffective-re<br>547 behaviors present in GluA1 546 schipped and (Fitzgerald, Barkus et al. 2019). Here we found that GluA1 CTD truncation alone recapitulated the schizoaffective-relevant<br>547 behaviors present in GluA1 KO mice. Specifically, the increase in approach beh 547 behaviors present in GluA1 KO mice. Specifically, the increase in approach behavior in the elevate<br>548 maze, light/dark transition and forced swim tests can be interpreted as reduced anxiety / depressi<br>549 but may also maze, light/dark transition and forced swim tests can be interpreted as reduced anxiety / depression,<br>549 but may also reflect increased novelty-seeking or risk-taking, recapitulating and even exacerbating<br>550 some of the 549 but may also reflect increased novelty-seeking or risk-taking, recapitulating and even exacerbating<br>550 some of the symptoms of schizophrenia and ADHD previously observed in constitutive GluA1 KOs.<br>551 Similar to genet 550 some of the symptoms of schizophrenia and ADHD previously observed in constitutive GluA1 KOs.<br>551 Similar to genetic deletion of GluA1, the behavioral consequences of GluA1 CTD truncation are com<br>552 and a complete, ac 551 Similar to genetic deletion of GluA1, the behavioral consequences of GluA1 CTD truncation are com<br>552 and a complete, accurate interpretation will require additional studies.<br>553 In summary, this study provides a compr Similar to genetic deletion of GluA1, the behavioral consequences of GluA1 CTD truncation are comp<br>352 and a complete, accurate interpretation will require additional studies.<br>353 In summary, this study provides a comprehe

556 dependent affective and memory processes. Our study identifies the GluA1 CTD as a crucial element in 553 AMPAR subunit levels, intracellular trafficking, cell type-specific synaptic transmission and GluA1-<br>556 AMPAR subunit levels, intracellular trafficking, cell type-specific synaptic transmission and GluA1-<br>557 the AMPAR c dependent affective and memory processes. Our study identifies the GluA1 CTD as a crucial eleme<br>557 the AMPAR complex that regulates the strength of excitatory synapses onto inhibitory INs, and<br>558 suggests that ΔCTD GluA 557 the AMPAR complex that regulates the strength of excitatory synapses onto inhibitory INs, and<br>558 suggests that  $\triangle CTD$  GluA1 mice may be valuable to study features of schizoaffective and other<br>559 psychiatric disorders 558 suggests that ACTD GluA1 mice may be valuable to study features of schizoaffective and other<br>559 sychiatric disorders.<br>560 Acknowledgments 559 sychiatric disorders.<br>560 supplements<br>561 Acknowledgments We would like to thank Dr. Roger Nicoll for supporting initial experiments in his laborate

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550 psychologie also<br>560 Acknowledgments<br>562 We would like<br>563 Mulatwa T. Haile and 561 Acknowledgments<br>1962 We would like to thank Dr. Roger Nicoll for supporting initial experiments in his laboratory. Dr. Mulatwa T. Haile and Dr. Lulu Y. Chen for guidance and equipment used in behavior assessments, and<br>1964 the Diaz-Alonso lab members for fruitful discussions. This work is supported by grants K99/Roo<br>1965 MH118425, Whitehal 1564 The Diaz-Alonso lab members for fruitful discussions. This work is supported by grants K99/Roo<br>1563 MH118425, Whitehall Foundation, Brain and Behavior Research Foundation and UCI start-up funds to<br>1566 J.D.-A. and AG0 565 MH118425, Whitehall Foundation, Brain and Behavior Research Foundation and UCI start-up full<br>566 J.D.-A. and AGo76835 to M.A.W. G.S. is supported a the T32 Training Program in Epilepsy Resea<br>567 (T32NS045540). C.A.C. i 566 J.D.-A. and AGo76835 to M.A.W. G.S. is supported a the T32 Training Program in Epilepsy Research<br>567 (T32NS045540). C.A.C. is supported by an HHMI Gilliam's Fellowship. A.M. is supported by the NIH-<br>568 NIGMS Maximizin 567 (T32NS045540). C.A.C. is supported by an HHMI Gilliam's Fellowship. A.M. is supported by the NIH-<br>568 MIGMS Maximizing Access to Research Careers T34 (#GM136489). M.A.S. is supported by a Eugene<br>569 Cota-Robles fellows 1986 NIGMS Maximizing Access to Research Careers T34 (#GM136489). M.A.S. is supported by a Eugene<br>569 Cota-Robles fellowship and the Howard Schneiderman T32 Training Program in Learning and Meme<br>570 (#T32MH119049). V.A.V. 569 Cota-Robles fellowship and the Howard Schneiderman T32 Training Program in Learning and Memo<br>570 (#T32MH119049). V.A.V. is supported by the NRSA DA059982 fellowship. The Optical Biology Core<br>571 Facility of the Develop 569 Cota-Robles fellowship and the Howard Schneiderman T32 Training Program in Learning and Memo<br>570 (#T32MH119049). V.A.V. is supported by the NRSA DA059982 fellowship. The Optical Biology Core<br>571 Facility of the Develop Facility of the Developmental Biology Center is supported by grants CA-62203 and GM-076516.  $572$ 

- 573 Author contributions 575 biochemistry experiments; G.S., A.V.K and M.A.S. performed and analyzed histology experiments; G.<br>576 A.V.K., C.A.C., A.M., V.A.V., I.L., J.S. and M.A.W. performed and analyzed behavior experiments; G.S<br>577 and J.D.-A. 576 A.V.K., C.A.C., A.M., V.A.V., I.L., J.S. and M.A.W. performed and analyzed behavior experiments; G.S.<br>577 and J.D.-A. drafted, and all authors edited the manuscript. J.D.-A. coordinated the study.<br>578 **Conflict of Inte** 576 A.V.K., C.A.C., A.M., V.A.V., I.L., J.S. and M.A.W. performed and analyzed behavior exper<br>577 and J.D.-A. drafted, and all authors edited the manuscript. J.D.-A. coordinated the study.<br>578 **Conflict of Interest**<br>580 Th
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### 582 Figure legends<br>583 Figure 1. AMPA

### 579 Commet of interest<br>580 The authors declare<br>581 Figure legends<br>583 Figure 1. AMPAR su 581<br>582 Figure legends<br>583 Figure 1. AMPAR subunit levels and subcell<br>584 CTD. 583 Figure 1. AMPAR subunit levels and subcellular distribution are affected by the loss of the GluA1  $304$  CTD.

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- 586 fractionation (left) and immunoblot from whole-brain lysate (WBL) and synaptosomal fractionation (left) and immunoblot from whole-brain lysate (WBL) and synaptosomal fractionation in 3587 and ΔCTD GluA1 (right). C-F: 587 and ΔCTD GluA1 (right). C-F: GluA1 (C), GluA2 (D), GluA3 (E), and GluA4 (F) levels normalized to α-<br>588 tubulin from WT WBL. G: GluA1 ATD staining (red) in WT and ΔCTD GluA1 hippocampus. H-I: Average<br>589 soma / dendri 587 and ∆CTD GluA1 (right). C-F: GluA1 (C), GluA2 (D), GluA3 (E), and GluA4 (F) levels normalized to α-<br>588 tubulin from WT WBL. G: GluA1 ATD staining (red) in WT and ∆CTD GluA1 hippocampus. H-I: Avera<br>590 soma / dendrit 589 soma / dendrite ratio of GluA1 signal in CA1 and DG, respectively. J: GluA2 staining (green) in WT and ∆CTD GluA1 hippocampus. K-L: Average soma/dendritic ratio of GluA2 in WT and ∆CTD GluA1 mice fo<br>591 hippocampal fi
- 589 soma / dendrite ratio of GluA1 signal in CA1 and DG, respectively. J: GluA2 staining (green) in WT and<br>590 ΔCTD GluA1 hippocampus. K-L: Average soma/dendritic ratio of GluA2 in WT and ΔCTD GluA1 mice for<br>591 hippocamp
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- 591 ∴ Fight community present in this system with the some in the some for the lender of GluA1 (red) and<br>592 ∂FSD-95 (cyan) in CA1 and DG in WT and ∆CTD GluA1 samples (top) and colocalization quantification<br>593 (bottom). 592 BSD-95 (cyan) in CA1 and DG in WT and ΔCTD GluA1 samples (top) and colocalization quantification<br>593 (bottom). O, P: Representative immunostaining of GluA2 (red) and GluA3 (cyan), in CA1 and DG in WT<br>594 and ΔCTD GluA 593 (bottom). O, P: Representative immunostaining of GluA2 (red) and GluA3 (cyan), in CA1 and DG in W<br>594 and ΔCTD GluA1 samples (top) and colocalization quantification (bottom). Q: Schematic of subcellular<br>595 distribut
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- 393 and ΔCTD GluA1 samples (top) and colocalization quantification (bottom). Q: Schematic of subcellular distribution of GluA1 and GluA2 in CA1 and DG in WT and ΔCTD GluA1 PNs. S.P., Stratum pyramidale;<br>596 S.R., Stratum 595 distribution of GluA1 and GluA2 in CA1 and DG in WT and ΔCTD GluA1 PNs. S.P., Stratum pyramidale;<br>596 S.R., Stratum radiatum; S.M., Stratum moleculare; S.G., Stratum granulare. Scale bar: G, J, 200 μm; M·<br>597 P, 10 μ 596 S.R., Stratum radiatum; S.M., Stratum moleculare; S.G., Stratum granulare. Scale bar: G, J, 200 μm; M.<br>597 P, 10 μm. Error bars represent SEM. n.s., not statistically different; \*, p≤0.05; \*\*, p≤0.01; \*\*\*, p≤0.001;<br>\* 596 S.R., Stratum radiatum; S.M., Stratum moleculare; S.G., Stratum granulare. Scale bar: G, J, 200 μm; M-<br>597 P, 10 μm. Error bars represent SEM. n.s., not statistically different; \*, p≤0.05; \*\*, p≤0.01; \*\*\*, p≤0.001;<br>\*
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### 597 P, 10 pm. Error bars represent SEM. n.s., not statistically different; γ, p⊆0.0<sub>5</sub>; γ, p⊆0.02, γ, p⊆0.02, p<br>598 P, +\*\*\*, p<0.0001. C-F: one-way ANOVA. H-P: unpaired t-test.<br>599 Figure 2. ΔCTD GluA1 mice exhibit novel 598 \*\*\*\*, p<0.0001. C-F: one-way ANOVA. H-P: unpaired t-test. 600 600 Figure 2. ∆CTD GluA1 mice exhibit novelty-induced hyperlocomotion and impaired fear expression,

602 But intact memory.<br>602 A: Mean distance tra<br>603 forced alternation Y-<br>604 WT and ΔCTD GluA1

603 forced alternation Y-maze task. C: Time in novel arm relative to total time n novel and familiar arms<br>604 WT and ∆CTD GluA1 mice. D: Representative track plots overlayed atop heat maps of WT (left) and<br>604 WT and ∆CT

604 Forced alternation Y-maze task. C: Time in novel arm relative to total time n novel and hand arms for WT<br>604 Forced alternation Y-maze task. D: Representative track plots overlayed atop heat maps of WT (left) and<br>604  $\mathcal{L}(\mathcal{A}) = \mathcal{L}(\mathcal{A}) = \mathcal{L}(\mathcal{A})$  microscopic track plots overlayed atop heat maps of  $\mathcal{L}(\mathcal{A})$  and

<u>COC An abituation for WT and ΔCTD GluA1 mice. F: Schematic of object location memory (OLM) task (left)</u><br>
and representative heat maps (right) of WT and ΔCTD GluA1 mice during training and test day. G:<br>
Discrimination in 607 and representative heat maps (right) of WT and ∆CTD GluA1 mice during training and test day. G:<br>608 Discrimination index during training and test sessions for WT and ∆CTD GluA1 mice in the OLM task.<br>609 Schematic of For a mandepertent of the theorem, engines the term is the form of MT and ∆CTD GluA1 mice in the OLM target Schematic of novel object recognition (NOR) task (left) and representative heat maps (right) of WT ∆CTD GluA1 mi Schematic of novel object recognition (NOR) task (left) and representative heat maps (right) of WT and ∆CTD GluA1 mice during training and test day. I: Discrimination index during training and test sessions for WT and ∆C 609 Schematic of novel object recognition (NOR) task (left) and representative heat maps (right) of WT and<br>610  $\,\Delta$ CTD GluA1 mice during training and test day. I: Discrimination index during training and test sessions<br>61 614 N: Freezing % across time (M) and average freezing % (N) during context recall test for WT and  $\triangle CTD$ Freezing during training (K) and during the 24-hour contextual recall (L) during contextual fear<br>613 conditioning for WT and ∆CTD GluA1 mice. Foot shocks are indicated with vertical red dashed lines. M,<br>614 N: Freezing % 613 conditioning for WT and ΔCTD GluA1 mice. Foot shocks are indicated with vertical red dashed<br>614 N: Freezing % across time (M) and average freezing % (N) during context recall test for WT and<br>615 GluA1 mice. Error bars 614 N: Freezing % across time (M) and average freezing % (N) during context recall test for WT and ΔCTD GluA1 mice. Error bars represent SEM. Empty dots represent females, filled dots represent males. n.s., not statistic 615 GluA1 mice. Error bars represent SEM. Empty dots represent females, filled dots represent males. n.s.<br>616 not statistically different; \*, p≤0.05; \*\*\*, p≤0.001; \*\*\*\*, p≤0.0001. A, E, K, M: two-way ANOVA. C:<br>617 unpaire not statistically different; \*, p≤0.05; \*\*\*, p≤0.001; \*\*\*\*, p≤0.0001. A, E, K, M: two-way ANOVA. C:<br>617 Gunpaired t-test. G, I: paired t-test. L: Mann-Whitney test. N: Welch's t test.<br>618 Figure 3. Pre-exposure to the cont 617 unpaired t-test. G, I: paired t-test. L: Mann-Whitney test. N: Welch's t test.<br>618 Figure 3. Pre-exposure to the context prior to fear conditioning partially rescues freezing behav<br>620 Figure 3. Pre-exposure to the co onpaired t-test. G, I: paired t-test. L: Mann-Whitney test. N: Welch's t test.<br>618 Figure 3. Pre-exposure to the context prior to fear conditioning partially rescues freezing behavior<br>620 in ΔCTD GluA1 mice.<br>621 A: Schema 618 619 Figure 3. Pre-exposure to the context prior to fear conditioning partially rescues freezing behavior 620 in ∆CTD GluA1 mice. A: Schematic of pre-exposure contextual fear conditioning for WT and ΔCTD GluA1 mice. Foot shocks are<br>623 indicated with vertical red dashed lines. Horizontal dashed line indicates baseline freezing (percentage<br>624 of tim or a strange freezing (C) during context free transformation in the indicates baseline freezing (percentage<br>624 of time spent freezing during the 5 min. prior to the first shock). D, E: Freezing % across time (D) and<br>625 624 of time spent freezing during the 5 min. prior to the first shock). D, E: Freezing % across time (D) and<br>625 average freezing % (E) during context recall test for WT and  $\triangle CTD$  GluA1 mice. Error bars represent<br>626 SEM. 624 of time spent freezing during the 5 min. prior to the first shock). D, E: Freezing % across time (D) and<br>625 average freezing % (E) during context recall test for WT and  $\triangle CTD$  GluA1 mice. Error bars represent<br>626 SEM 626 SEM. Empty dots represent females, filled dots represent males. n.s., not statistically different; \*\*,<br>627 p≤0.01. B, D: two-way ANOVA. C: Mann-Whitney test. E: Welch's t-test.<br>628 Figure 4. ΔCTD GluA1 mice recapitul

### 627 SEM. Empty dots represent females, must be represent male male, must film, since they are proton, procedure<br>628 Sigure 4. ACTD GluA1 mice recapitulate additional behavioral features of germline GluA1 knock<br>630 Sigure 4 628 p=0.01. B, D: two-way ANOVA. Statem Whitney test. E: Welch's tiest.<br>629 prigure 4. ACTD GluA1 mice recapitulate additional behavioral feature.<br>631 A: Schematic of elevated plus maze. B-D: Mean percentage of time spen 628<br>629 629 Figure 4. ∆CTD GluA1 mice recapitulate additional behavioral features of germline GluA1 knockout

- 630 mice.<br>631 A: Schematic of elevated plus maze. B-D: Mean percentage of time spent in open arms (B), total
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- Fig. 2018. The substitute plus masses is a comparison of entries into the closed arms (D) for<br>632 A: Momber of entries into the open arms (C) and total number of entries into the closed arms (D) for<br>634 Compartment for WT and ΔCTD GluA1 mice. E: Schematic of light/dark box paradigm. F: Mean latency to enter the dark<br>634 compartment for WT and ΔCTD GluA1. G: Schematic of forced swim test. H: Mean time spent immot<br>635 for WT and ΔCTD GluA1 m
- o and ∆CTD GluA1 mice. E: Schematic of light/dark box paradigm. F: Mean latency to enter the dark<br>1934 compartment for WT and ∆CTD GluA1. G: Schematic of forced swim test. H: Mean time spent immobile<br>1935 for WT and ∆CTD
- for WT and ∆CTD GluA1 mice. Error bars represent SEM. Empty dots represent females, filled dots  $\mathcal{L}(\mathcal{$

637 Figure Males. N.s., Notificially different; \*, p≤0.05; \*, p≤0.000; \*, p≤0.0001; \*, p≤0.0001; \*, p≤0.0001;<br>638 Figure 5. Exacerbated DG GC activation in ΔCTD GluA1 mice following open field exposure.<br>640 A: Schematic o

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### 639 Figure 5. Exacerbated DG GC activation in ∆CTD GluA1 mice following open field exposure.

- 638<br>639 Figure 5. Exacerbated DG GC acti<br>640 A: Schematic of open field experin<br>641 hours in the open field arena in WT For a maximizer of parameter of parameters of operational and parameters and parameters in the open field arena in WT and  $\triangle CTD$  GluA1 mice. B: representative c-Fos staining (red) in WT<br>and  $\triangle CTD$  GluA1 hippocampus. C-E:
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- 642 and ∆CTD GluA1 hippocampus. C-E: Average number of c-Fos-positive cells in the dentate gyrus<br>643 granule layer, CA<sub>3</sub>, and CA1, respectively. Error bars represent SEM. Empty dots represent females,<br>644 filled dots re G43 granule layer, CA3, and CA1, respectively. Error bars represent SEM. Empty dots represent femal<br>644 filled dots represent males. Scale bar: 200 μm. \*\*, p≤0.01; \*\*\*, p≤0.001; \*\*\*\*, p≤0.0001, one-wa<br>645 ANOVA.<br>646 granule layer, CA<sub>3</sub>, and CA1, respectively. Error bars represent SEM. Empty dots represent females<br>644 filled dots represent males. Scale bar: 200 µm. \*\*, p≤0.01; \*\*\*, p≤0.001; \*\*\*\*, p≤0.0001, one-way<br>645 ANOVA.<br>647 **Figu**
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### 645 filled and dots represent males. Scale bar: 200 pc. 11, p=0.01, p=0.011; p≤0.011; p≤0.011; ANOVA.<br>646 figure 6. Intact excitatory synaptic transmission and LTP in DG granule cells but altered excitations of the synapt ---<br>646<br>647 Figure 6.<br>648 synaptic<br>649 A: Whole 647 Figure 6. Intact excitatory synaptic transmission and LTP in DG granule cells but altered excitatory 648 synaptic transmission in DG inhibitory INs in ∆CTD GluA1 mice.<br>649 A: Whole-cell patch-clamp recording set-up for slice electrophysiology experiments in DG granule cells

650 (GCs). B: Average paired-pulse ratio (PPR) values for evoked AMPAR EPSCs in WT and  $\Delta$ CTD GluA1 GCs.<br>651 Representative WT (blue) and  $\Delta$ CTD GluA1 (yellow) traces are shown to the right of the plot. C: Average<br>652 A 651 Representative WT (blue) and ∆CTD GluA1 (yellow) traces are shown to the right of the plot. C: Average<br>652 AMPAR/NMDAR ratios in WT and ∆CTD GluA1 GCs. D: Input-output relationship plot of AMPAR EPSCs<br>653 in WT and ∆ 652 AMPAR/NMDAR ratios in WT and ∆CTD GluA1 GCs. D: Input-output relationship plot of AMPAR EPSCs<br>653 in WT and ∆CTD GluA1 DG GCs. Representative WT (blue) and ∆CTD GluA1 (yellow) traces are shown<br>654 to the right of the 653 AMPAR REPSC amplitude before the source of AMPAR CTD GluA1 (yellow) traces are shown<br>654 to the right of the plot. E: AMPAR EPSC amplitude of WT and ∆CTD GluA1 DG GCs normalized to the<br>655 mean AMPAR EPSC amplitude b to the right of the plot. E: AMPAR EPSC amplitude of WT and ∆CTD GluA1 DG GCs normalized to the<br>655 mean AMPAR EPSC amplitude before theta-burst LTP induction (arrow). Representative WT (blue) an<br>656 ∆CTD GluA1 (yellow) for the right of the plot. E: All plots of the right of the plot. In the 2002 Depresentative WT (blue) are discussed.<br>656 ΔCTD GluA1 (yellow) traces are shown to the right of the plot. n indicates number of cells induced 656 ΔCTD GluA1 (yellow) traces are shown to the right of the plot. n indicates number of cells induced /<br>657 mumber of cells at the end of the experiment (min. 40). F: Whole-cell patch-clamp recording set-up for<br>658 slice Note that the end of the experiment (min. 40). F: Whole-cell patch-clamp recording set-up<br>658 Sice electrophysiology experiments in DG INs. WT and ΔCTD GluA1 mice were stereotaxically inject<br>659 (AAV-mDLX-GFP) to label I 658 slice electrophysiology experiments in DG INs. WT and ΔCTD GluA1 mice were stereotaxically injected<br>659 (AAV-mDLX-GFP) to label INs in DG. G: Mean values of AMPAR/NMDAR ratios in WT and ΔCTD GluA1<br>660 mDLX-GFP(+)-labe 658 slice electrophysiology experiments in DG INs. WT and ∆CTD GluA1 mice were stereotaxically injected<br>659 (AAV-mDLX-GFP) to label INs in DG. G: Mean values of AMPAR/NMDAR ratios in WT and ∆CTD GluA1<br>660 mDLX-GFP(+)-lab 661 right of the plot. Error bars represent SEM. Scale bars: 5opA, 2oms. n.s., not statistically different; \*,<br>662 p≤o.o5. B-C, E, G: unpaired t-test. D: two-way ANOVA.<br>663 for the string of the plot. Error bars represent SEM. Scale bars: 50pA, 20ms. n.s., not statistically different; \*,<br>662 p≤0.05. B-C, E, G: unpaired t-test. D: two-way ANOVA.<br>663 Suppl. Figure 1. Analysis of excitatory sy right of the plot. Error bars represent Sem. Superint Sem. 3. pp. 4. Entertain, and statistically p<br>662 p≤0.05. B-C, E, G: unpaired t-test. D: two-way ANOVA.<br>664 Suppl. Figure 1. Analysis of excitatory synapse density in 663<br>664 Suppl. Figure 1. Analysis of excitatory synapse densit<br>665 A-B: Average density of GluA1 and PSD-95 positive pun<br>666 and PSD-95 positive puncta in DG ML. E-F: Average der

663 664 Suppl. Figure 1. Analysis of excitatory synapse density in CA1 and DG in WT and ∆CTD GluA1 mice.

665 A-B: Average density of GluA1 and PSD-95 positive puncta in CA1 SR. C-D: Average density of GluA1<br>666 and PSD-95 positive puncta in DG ML. E-F: Average density of GluA2 and GluA3 positive puncta in CA1

effects in DSD-95 positive puncta in DG ML. E-F: Average density of GluA2 and GluA3 positive puncta in Ca1<br>Average density of GluA2 and GluA3 positive puncta in CA1 positive puncta in CA1 positive puncta in CA1 positi<br>Aver

668 non-statistically significant; \*, p≤0.05, unpaired t-test.<br>669 Suppl. Figure 2. Control behavioral assessments in WT and ΔCTD GluA1 mice (related to Fig. 2).<br>671 A-C: Average thigmotaxis (A), fine movements (B), and r 669 non-statistically significant; \*, p⊆0.0<sub>5</sub>, onpaired t-test.<br>669 **Suppl. Figure 2. Control behavioral assessments in W**<br>671 A-C: Average thigmotaxis (A), fine movements (B), and<br>672 during an open field test. D: Total 669<br>670 670 Suppl. Figure 2. Control behavioral assessments in WT and ∆CTD GluA1 mice (related to Fig. 2).<br>671 A-C: Average thigmotaxis (A), fine movements (B), and rearings (C) of WT and ∆CTD GluA1 male mi 672 during an open field test. D: Total distance travelled of WT, heterozygous, and homozygous ΔCTD<br>673 GluA1 female and male mice in the open field test. E-F: Mean distance traveled during training (E) and<br>674 test (F) 673 GluA1 female and male mice in the open field test. E-F: Mean distance traveled during training (E) a<br>674 test (F) for WT and CTD GluA1 mice in the OLM task. G-H: Mean object exploration time during training<br>675 (G) an test (F) for WT and CTD GluA1 mice in the OLM task. G-H: Mean object exploration time during training<br>675 (G) and test (H) for WT and CTD GluA1mice in the OLM task. I-J: Mean distance traveled during training<br>676 (I) and t 675 (G) and test (H) for WT and CTD GluA1 mice in the OLM task. I-J: Mean distance traveled during training<br>676 (I) and test (J) for WT and CTD GluA1 mice in NOR task. K-L: Mean object exploration time during<br>677 training (I) and test (J) for WT and CTD GluA1 mice in NOR task. K-L: Mean object exploration time during<br>676 (I) and test (J) for WT and CTD GluA1 mice in NOR task. M: Linear regression of total distance<br>678 traveled (meters) and 677 (Interactive) and test (L) for WT and CTD GluA1 mice in NOR task. M: Linear regression of total dist<br>678 (Interaction of total discrimination index during OLM test day. N: Linear regression of total object exploration traveled (meters) and discrimination index during OLM test day. N: Linear regression of total object<br>exploration (seconds) and discrimination index during OLM test day. O: Average hind paw withdrawal<br>680 latency of WT and exploration (seconds) and discrimination index during OLM test day. O: Average hind paw withdraw<br>680 latency of WT and CTD GluA1 mice in the hot plate test. P: Average motion index of WT and ΔCTD<br>681 GluA1 mice during con 680 latency of WT and CTD GluA1 mice in the hot plate test. P: Average motion index of WT and ΔCTD<br>681 GluA1 mice during contextual fear conditioning (arbitrary units). Q: Linear regression of percentage of<br>682 freezing d 681 GluA1 mice during contextual fear conditioning (arbitrary units). Q: Linear regression of percentage freezing during conditioning (10 min) and recall (8 min). R: Average percentage of freezing measure across time (mi Freezing during conditioning (10 min) and recall (8 min). R: Average percentage of freezing measured<br>683 across time (minutes) during the fear generalization test for WT and ΔCTD GluA1 mice. S: Average<br>684 percentage of f across time (minutes) during the fear generalization test for WT and ΔCTD GluA1 mice. S: Average<br>684 percentage of freezing during the fear generalization test for WT and ΔCTD GluA1 mice. Error bars<br>685 represent SEM. Em of the factor and spiritually during the fear generalization test for WT and ∆CTD GluA1 mice. Error bars<br>685 represent SEM. Empty dots represent females, filled dots represent males. n.s. not statistically diffe<br>686 \*p≤0 For a percentage of freezing arrangemental generalization test for formulation tends for the formulation of the fe<br>686 percentage of freezing during the fear generalization test for Multiple s. n.s. not statistically diff the statistic set of the set of the statistic set of the statistic matter in the statistic statistic set of the<br>686 <sup>\*</sup> p≤0.05, \*\*\*p≤0.001. A, B, H, O, S: Welch's t test. C, I, J, K: Mann-Whitney test. D: one-way ANOVA.

687 G, L: unpaired t-test. M, N, Q: Linear regression. P: multiple t design. R: two-way ANOVA.<br>688 Suppl. Figure 3. Shock reactivity of WT and ΔCTD GluA1 mice in contextual fear conditioning<br>690 Paradigm. 688 G, L: External strain, M, C. Linear regression. P: Maring traing in the Viet, P: M;<br>689 G, Suppl. Figure 3. Shock reactivity of WT and ΔCTD GluA1 mice in contextual fear condition<br>691 Average motion index of WT and ΔC 688 689 Suppl. Figure 3. Shock reactivity of WT and ∆CTD GluA1 mice in contextual fear conditioning

690 paradigm.<br>691 Average motion index of WT and ACTD GluA1 mice during contextual fear conditioning (arbitrary units). 692 From bars represent SEM. Empty dots represent females, filled dots represent males. Non-statistically<br>693 Significant differences, two-way ANOVA.<br>694 Suppl. Figure 4. Control behavioral assessments in WT and ∆CTD Glu

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693 Significant differences, two-way ANOVA.<br>693 Significant differences, two-way ANOVA.<br>695 Suppl. Figure 4. Control behavioral assessments in WT and ΔCTD GluA1 mice (related to Fig. 4).<br>696 A: Average time spent in the o 1986<br>694 Suppl. Figure 4. Control behavioral asses<br>696 A: Average time spent in the open arms as<br>697 GluA1 mice. B: Ratio of distance traveled i Supple 4. Control behavioral assessments in WT and ∆CTD GluA1 mice (related to Fig. 4).<br>696 A: Average time spent in the open arms across time during the elevated plus maze for WT and ∆CTD<br>697 GluA1 mice. B: Ratio of dis 697 GluA1 mice. B: Ratio of distance traveled in open arms relative to total distance traveled during the elevated plus maze for WT and ∆CTD GluA1 mice. C: Average distance traveled in the closed arms<br>698 elevated plus m 698 elevated plus maze for WT and ΔCTD GluA1 mice. C: Average distance traveled in the closed arms elevated plus maze for WT and ΔCTD GluA1 mice. C: Average distance traveled in the closed arms elevated plus maze for WT and ∆CTD GluAn mice. C: Average distance traveled in the closed arms of WT and ∆CTD G<br>The closed arms of WT and ∆CTD GluAn microsed arms of the closed arms of the closed arms of the closed arms o

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- 6999 to all marge the elevated plus maze for WT and ∆CTD GluA1 mice. E: Average time spent in the light zone of the<br>1999 during the light/dark alternation test for WT and ∆CTD GluA1 mice. F: Average latency to immobility 1.1 light/dark alternation test for WT and ∆CTD GluA1 mice. F: Average latency to immobility during the<br>1702 forced swim test for WT and ∆CTD GluA1 mice. Error bars represent SEM. Empty dots represent<br>1703 females, fille 702 forced swim test for WT and ∆CTD GluA1 mice. Error bars represent SEM. Empty dots represent<br>703 females, filled dots represent males. n.s., non-statistically significant; \*\*, p≤0.01, \*\*\*\*, p≤0.0001, A:<br>704 two-way AN
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## 703 females, filled dots represent males. n.s., non-statistically significant; \*\*, p≤0.01, \*\*\*\*, p≤0.000<br>704 two-way ANOVA. B-D: Welch's t-test. E: Mann-Whitney test. F: unpaired t-test.<br>705 Suppl Figure 5. c-Fos analysi 704 females, filled dots represent males. n.e., non-statistically significally filled dots represent the two-way ANOVA. B-D: Welch's t-test. E: Mann-Whitney test. F: unpaired t-test.<br>705<br>706 Suppl Figure 5. c-Fos analysis 705<br>706 Suppl Figure 5. c-Fos analysis in various brain regions of WT and ΔCTD GluA1<br>707 field exposure.<br>708 A: Schematic of experimental timeline. B: c-Fos staining (red) of representative \ 706 Suppl Figure 5. c-Fos analysis in various brain regions of WT and ∆CTD GluA1 mice following open

- 707 field exposure.<br>708 A: Schematic of experimental timeline. B: c-Fos staining (red) of representative WT and ΔCTD GluA1
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- 909 mouse brains showing habenula, somatosensory cortex, subthalamic nucleus, and amygdala. C: c-Fos<br>100 staining (red) of representative WT and ∆CTD GluA1 mouse brains showing prefrontal cortex. D: c-Fos<br>111 staining (r 1099 staining (red) of representative WT and ΔCTD GluA1 mouse brains showing prefrontal cortex. D: c-Fos<br>111 staining (red) of representative WT and ΔCTD GluA1 mouse brains showing motor cortex, striatum, and<br>121 nucleus
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- 11 staining (red) of representative WT and ∆CTD GluA1 mouse brains showing motor cortex, striatum, and<br>12 nucleus accumbens. Error bars represent SEM. Error bars represent SEM. Empty dots represent female<br>13 filled dots
- 112 nucleus accumbens. Error bars represent SEM. Error bars represent SEM. Empty dots represent females,<br>
713 filled dots represent males. n.s., not statistically different; \*, p≤0.05; \*\*, p≤0.01; \*\*\*, p≤0.001; \*\*\*\*,<br>
714 filled dots represent males. n.s., not statistically different; \*,  $p \le 0.05$ ; \*\*,  $p \le 0.01$ ; \*\*\*,  $p \le 0.001$ ; \*\*\*\*,
- 714 filmed dots represent males. n.s., not statistically different; \*, p⊆0.05; \*, p⊆0.0001; \*, p≤0.0001; \*<br>715<br>716<br>717
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# 715<br>715<br>716<br>717<br>718 <u>References</u> 718

719 Aitta-Aho, T<br>719 Aitta-Aho, T<br>720 Induced Hyp<br>721 <u>Front Pharm</u><br>723 Akgul, G. an<br>724 interneuron Aitta-Aho, T., M. Maksimovic, K. Dahl, R. Sprengel and E. R. Korpi (2019). "Attenuation of Novelty-<br>
720 Induced Hyperactivity of Gria1-/- Mice by Cannabidiol and Hippocampal Inhibitory Chemogenetics."<br>
721 <u>Front Pharmaco</u>

- 
- 120 Induced Hyperactivity of Critics (Micela) Chemokratic Histophysical Hyperactivity of Grian-1722<br>122 Akgul, G. and C. J. McBain (2016). "Diverse roles for ionotropic glutamate receptors on inhibitory<br>124 Interneurons in 121 Front Pharmacol 10: 309.<br>122 Akgul, G. and C. J. McBair<br>124 Fritherneurons in developin<br>125 Ancona Esselmann, S. G., 127 homeostasis requires the 722
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- 724 Aktor and Muslem Muslem (2017). The United States of the United States interneurons in developing and adult brain." <u>J Physiol 594(19): 5471-5490.</u><br>725 Ancona Esselmann, S. G., J. Diaz-Alonso, J. M. Levy, M. A. Bemben 724 Interneurons in developing and adult brain. <u>31 hysiol 594(19): 5471-5490.</u><br>725 Ancona Esselmann, S. G., J. Diaz-Alonso, J. M. Levy, M. A. Bemben and R.<br>727 Interneuralis requires the membrane-proximal carboxy tail of 725
- - 729
	-
- 727 homeostasis requires the membrane-proximal carboxy tail of GluA2." <u>Proc Natl Acad Sci U S A</u> 114(5<br>728 13266-13271.<br>729 Bannerman, D. M., T. Borchardt, V. Jensen, A. Rozov, N. N. Haj-Yasein, N. Burnashev, D. Zamanillo
- 727 Franciscass requires the membrane-proximal carboxy tail of GloA2. <u>Froc Natl Acad Sci U S A</u> 114(50).<br>729 Bannerman, D. M., T. Borchardt, V. Jensen, A. Rozov, N. N. Haj-Yasein, N. Burnashev, D. Zamanillo, T.<br>731 Bus, I 729<br>729 Bannerman, I<br>731 Bus, I. Grube,<br>732 AMPA Recept<br>733 Bannerman, I 805, 1. Grube, G. Adelmann, J. N. P. Rawlins and R. Sprengel (2018). "Somatic Accumulation of GluA1-<br>
732 AMPA Receptors Leads to Selective Cognitive Impairments in Mice." <u>Front Mol Neurosci</u> 11: 199.<br>
733 Bannerman, D. M 2007). The Every Prince and Structure in the University of Content of Content of Content of Content of Content<br>231 Bannerman, D. M., R. M. Deacon, S. Brady, A. Bruce, R. Sprengel, P. H. Seeburg and J. N. Rawlins<br>235 (2004)
	- 732 AMPA Receptors Leads to Selective Cognitive Impairments in Mice. <u>Front Mol Neorosci</u> 11: 199.<br>733 Bannerman, D. M., R. M. Deacon, S. Brady, A. Bruce, R. Sprengel, P. H. Seeburg and J. N. Rawlins<br>735 (2004). "A compari 733
	- (2004). "A comparison of GluR-A-deficient and wild-type mice on a test battery assessing sensorimotor,
	- 736 affective, and cognitive behaviors." <u>Behav Neurosci</u> 118(3): 643-647.  $736$  affective, and cognitive behaviors."  $\frac{\text{Bernav Neoroscr}}{\text{BernavNeoroscr}}$  118(3): 043-047.







879 Andersen, O. Hvalby, B. Sakmann, P. H. Seeburg and R. Sprengel (2003). "A juvenile form of<br>879 Andersen, O. Hvalby, B. Sakmann, P. H. Seeburg and R. Sprengel (2003). "A juvenile form of  $\mathcal{S}_1$  . And the proof of the set  $\mathcal{S}_2$  and R. Seeburg and R. Sprengel (2003). "A just and R. Sprengel (2003). "A juvenile form of the set of the se

881 GluR-A." <u>J Physiol 553</u>(Pt 3): 843-856.<br>882 Kauer, J. A., R. C. Malenka and R. A. Nicoll (1988). "A persistent postsynaptic modification mediates<br>884 Iong-term potentiation in the hippocampus." <u>Neuron</u> 1(10): 911-917 882<br>883 Kauer, J. A., R. C. Malenka and R. A. N<br>884 Iong-term potentiation in the hippoca<br>885 Kay, Y., L. Tsan, E. A. Davis, C. Tian, L<br>887 Kanoski and B. E. Herring (2022). "Sch 882<br>883 884 Francon, J. A., R. A. Davis, C. Tian, L. Decarie-Spain, A. Sadybekov, A. N. Pushkin, V. Katritch, S. E.<br>885 Kay, Y., L. Tsan, E. A. Davis, C. Tian, L. Decarie-Spain, A. Sadybekov, A. N. Pushkin, V. Katritch, S. E.<br>887 885<br>885 Kay, Y., L. Tsan, E. A. Davis, C. Tian, L. Decarie-Spain, A. Sadybekov, Kanoski and B. E. Herring (2022). "Schizophrenia-associated SAP97 r<br>888 Synapse strength in the dentate gyrus and impair contextual episodic<br>8 885 887 Kanoski and B. E. Herring (2022). "Schizophrenia-associated SAP97 mutations increase glutamatergi<br>888 Synapse strength in the dentate gyrus and impair contextual episodic memory in rats." <u>Nat Commun</u><br>890 Kerr, J. M. a 888 Synapse strength in the dentate gyrus and impair contextual episodic memory in rats." <u>Nat Commun</u><br>889 13(1): 798.<br>890 Kerr, J. M. and T. A. Blanpied (2012). "Subsynaptic AMPA receptor distribution is acutely regulated 888 synapse strength in the dentate gyrus and impair contextual episodic memory in rats." <u>Nat Commun</u><br>889 **1** 13(1): 798.<br>890 Kerr, J. M. and T. A. Blanpied (2012). "Subsynaptic AMPA receptor distribution is acutely regul 889<br>890 Kerr, J. M.<br>892 actin-drive<br>893 Kim, C. H.,<br>895 (2005). "Pe 891 892 Actin-driven reorganization of the postsynaptic density." <u>J Neurosci</u> 32(2): 658-673.<br>893<br>894 Kim, C. H., K. Takamiya, R. S. Petralia, R. Sattler, S. Yu, W. Zhou, R. Kalb, R. Wenthold and R. Huganir<br>895 (2005). "Persi 892 actin-driven reorganization of the postsynaptic density." J Neurosci 32(2): 658-673. 893 1995 (2005). "Persistent hippocampal CA1 LTP in mice lacking the C-terminal PDZ ligand of GluR1." <u>Nat</u><br>896 (2005). "Persistent hippocampal CA1 LTP in mice lacking the C-terminal PDZ ligand of GluR1." <u>Nat</u><br>897 Lee, H. K., 896 Neurosci 8(8): 985-987.<br>897 Lee, H. K., K. Takamiya, J. S. Han, H. Man, C. H. Kim, G. Rumbaugh, S. Yu, L. Ding, C. He, R. S. Petralia,<br>899 R. J. Wenthold, M. Gallagher and R. L. Huganir (2003). "Phosphorylation of the 897<br>898 Lee, H. K., K. Takamiya,<br>898 Lee, H. K., K. Takamiya,<br>899 R. J. Wenthold, M. Galla<br>900 subunit is required for sy<br>901 Lisman, J. E., J. T. Coyle 898 899 R. J. Wenthold, M. Gallagher and R. L. Huganir (2003). "Phosphorylation of the AMPA receptor GluR1<br>800 subunit is required for synaptic plasticity and retention of spatial memory." <u>Cell</u> 112(5): 631-643.<br>901 Lisman, J 880 Subunit is required for synaptic plasticity and retention of spatial memory." <u>Cell</u> 112(5): 631-643.<br>8901<br>8902 Lisman, J. E., J. T. Coyle, R. W. Green, D. C. Javitt, F. M. Benes, S. Heckers and A. A. Grace (2008).<br>803 900 subonit is required for synaptic plasticity and retention or spatial memory. <u>Cell</u> 112(5): 031-043.<br>901 Lisman, J. E., J. T. Coyle, R. W. Green, D. C. Javitt, F. M. Benes, S. Heckers and A. A. Grace (2008)<br>903 "Circui 902 903 Figure 1. Exception of synaptic AMPA receptors revealed by a single-cell genetic approach." Next USDS Contained Schizophrenia." <u>Trends Neurosci</u> 31(5): 234-242.<br>905 Lu, W., Y. Shi, A. C. Jackson, K. Bjorgan, M. J. Dur 904 Schizophrenia." <u>Trends Neurosci</u> 31(5): 234-242.<br>905 Lu, W., Y. Shi, A. C. Jackson, K. Bjorgan, M. J. During, R. Sprengel, P. H. Seeburg and R. A. N.<br>907 "Subunit composition of synaptic AMPA receptors revealed by a s 905<br>906 Lu, W., Y. Shi, A. C. Jackson, K. Bjorgan, M. J. Du<br>907 "Subunit composition of synaptic AMPA recepto<br>908 62(2): 254-268.<br>909 Luchkina, N. V., S. K. Coleman, J. Huupponen, C. 905<br>906 907 Fisibunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach." <u>Neuron</u><br>908 62(2): 254-268.<br>909 Luchkina, N. V., S. K. Coleman, J. Huupponen, C. Cai, A. Kivisto, T. Taira, K. Keinanen and 908 62(2): 254-268.<br>909 Luchkina, N. V., S. K. Coleman, J. Huupponen, C. Cai, A. Kivisto, T. Taira, K. Keinanen and S. E. Lauri<br>910 Luchkina, N. V., S. K. Coleman, J. Huupponen, C. Cai, A. Kivisto, T. Taira, K. Keinanen an 909<br>909<br>910 Luchkina, N. V.,<br>911 (2017). "Molecul<br>912 receptors critica<br>913 **112**(Pt A): 46-56<br>914 909<br>910 911 (2017). "Molecular mechanisms controlling synaptic recruitment of GluA4 subunit-containing AMPA-<br>912 (2017). "Molecular mechanisms controlling synaptic recruitment of GluA4 subunit-containing AMPA-<br>913 112(Pt A): 46-56 911 (2017). "Molecular mechanisms controlling synaptic recruitment of GluA4 subunit-containing AMPA-<br>912 receptors critical for functional maturation of CA1 glutamatergic synapses." <u>Neuropharmacology</u><br>913 **112**(Pt A): 46-913 receptors critical for functional material for the grotamatergics, nepsetim<u>ics in prespiramator of</u><br>914 Malinow, R. and R. C. Malenka (2002). "AMPA receptor trafficking and synaptic plasticity." <u>Annu F</u><br>916 Meurosci 913 112(PCA): 40-50.<br>914 Malinow, R. and F<br>916 <u>Neurosci</u> 25: 103-1<br>917 Marin, O. (2012).<br>919 915 916 Meurosci 25: 103-126.<br>917 Marin, O. (2012). "Interneuron dysfunction in psychiatric disorders." <u>Nat Rev Neurosci</u> 13(2): 107-120.<br>919 Martin, S. J., P. D. Grimwood and R. G. Morris (2000). "Synaptic plasticity and mem 917<br>918 Marin, O. (2012). "Inte<br>919 Martin, S. J., P. D. Grir<br>921 the hypothesis." <u>Annu</u><br>922 918 919<br>920 Martin, S. J., P. D. Grimwood and R. G. Morris (2000). "Synaptic plasticity and memory: an evaluation of<br>921 the hypothesis." <u>Annu Rev Neurosci</u> 23: 649-711.<br>923 Muller, D., M. Joly and G. Lynch (1988). "Contribut 920 921 Martin, Star Johnn Review Neurosci 23: 649-711.<br>922 Muller, D., M. Joly and G. Lynch (1988). "Contributions of quisqualate and NMDA receptors to the<br>924 Muller, D., M. Joly and G. Lynch (1988). "Contributions of quisqu 922<br>923 Muller, D., M. Joly and G. Lynch (1988). "Contributed<br>924 induction and expression of LTP." <u>Science</u> 242(48<br>925 Nicoll, R. A. (2017). "A Brief History of Long-Term<br>927 922 924 Muller, D., M. Joseph Christopher Christopher Christopher Christopher Christopher Christopher Christopher<br>925<br>926 Micoll, R. A. (2017). "A Brief History of Long-Term Potentiation." <u>Neuron 93(2): 281-290.</u><br>927 924 induction and expression of LTP." Science 242(4886): 1694-1697. 925 927 Nicoll, R. A. (2017). "A Brief History of Long-Term Potentiation." <u>Neuron 93(</u>2): 201-290."<br>927

- 
- 
- 
- 929 Harrison, M. E. Walton and D. M. Bannerman (2023). "Glutamatergic dysfunction leads to a hyper-<br>930 Harrison, M. E. Walton and D. M. Bannerman (2023). "Glutamatergic dysfunction leads to a hyper-<br>931 Salience." <u>Mol Ps</u> 930 Harrison, Maria Britannia, M. E. M. E. Marrison, M. Banner and Salience." <u>Mol Psychiatry</u> 28(2): 579-587.<br>931 Salience." <u>Mol Psychiatry</u> 28(2): 579-587.<br>932 Pelkey, K. A., R. Chittajallu, M. T. Craig, L. Tricoire, J. 931 salience." <u>Mol Psychiatry</u> 28(2): 579-587.<br>932 Pelkey, K. A., R. Chittajallu, M. T. Craig, L. Tricoire, J. C. Wester and C. J. McBain (2017). "Hippoc<br>934 GABAergic Inhibitory Interneurons." <u>Physiol Rev</u> 97(4): 1619-1 932
- 
- salience." <u>Mol Psychiatry</u> 28(2): 579-587.<br>
932 Pelkey, K. A., R. Chittajallu, M. T. Craig, L. Tricoire, J. C. Wester and C<br>
934 GABAergic Inhibitory Interneurons." <u>Physiol Rev</u> 97(4): 1619-1747.<br>
935 Procaccini, C., T. 934 GABAergic Inhibitory Interneurons." <u>Physiol Rev</u> 97(4): 1619-1747.<br>935<br>936 Procaccini, C., T. Aitta-aho, K. Jaako-Movits, A. Zharkovsky, A. Panhelainen, R. Sprengel, A. M. Linden<br>937 and E. R. Korpi (2011). "Excessive 935<br>936 Procaccini, C., T. Aitta-aho, K. Jaako-Movits, A. Zharkovsky, A. Par<br>937 and E. R. Korpi (2011). "Excessive novelty-induced c-Fos expressior<br>938 hippocampus of GluA1 knockout mice." <u>Eur J Neurosci</u> 33(1): 161-11<br>9 935
- 
- and E. R. Korpi (2011). "Excessive novelty-induced c-Fos expression and altered neurogenesis in the<br>
938 hippocampus of GluA1 knockout mice." <u>Eur J Neurosci</u> 33(1): 161-174.<br>
940 Reisel, D., D. M. Bannerman, W. B. Schmitt 938 bippocampus of GluA1 knockout mice." <u>Eur J Neurosci</u> 33(1): 161-174.<br>939 Reisel, D., D. M. Bannerman, W. B. Schmitt, R. M. Deacon, J. Flint, T. Borchardt, P. H. Seeburg and J<br>941 Rawlins (2002). "Spatial memory dissoc 939<br>939 Reisel, D., D. M. Bannerman, W. B. Schmitt, R. M. Deacon, J. Flint, T. F<br>941 Rawlins (2002). "Spatial memory dissociations in mice lacking GluR1."<br>942 Ripke, S., C. O'Dushlaine, K. Chambert, J. L. Moran, A. K. Kahl 940 941 Rawlins (2002). "Spatial memory dissociations in mice lacking GluR1." <u>Nat Neurosci</u> 5(9): 868-873.<br>942 Ripke, S., C. O'Dushlaine, K. Chambert, J. L. Moran, A. K. Kahler, S. Akterin, S. E. Bergen, A. L. Collins, J<br>944
- 942
- 942<br>942 Ripke, S., C. O'Dushlaine, K. Chambert, J. L. Moran, A. K. Kahler, S. Akterin, S. E. Bergen, A. L. Co<br>944 J. Crowley, M. Fromer, Y. Kim, S. H. Lee, P. K. Magnusson, N. Sanchez, E. A. Stahl, S. Williams, N.<br>945 Wray
- 
- 
- 
- 943 Ripke, S., C. O'Dushlaine, K. Chambert, J. L. Moran, A. K. Kahler, S. Akterin, S. E. Bergen, A. L. Collins, J.<br>944 J. Crowley, M. Fromer, Y. Kim, S. H. Lee, P. K. Magnusson, N. Sanchez, E. A. Stahl, S. Williams, N. R.<br> Wray, K. Xia, F. Bettella, A. D. Borglum, B. K. Bulik-Sullivan, P. Cormican, N. Craddock, C. de Leeuw,<br>946 Durmishi, M. Gill, V. Golimbet, M. L. Hamshere, P. Holmans, D. M. Hougaard, K. S. Kendler, K. Lin, D<br>947 Morris, O. 946 Durmishi, M. Gill, V. Golimbet, M. L. Hamshere, P. Holmans, D. M. Hougaard, K. S. Kendler, K. Lin, D. W.<br>947 Morris, O. Mors, P. B. Mortensen, B. M. Neale, F. A. O'Neill, M. J. Owen, M. P. Milovancevic, D.<br>948 Posthuma Morris, O. Mors, P. B. Mortensen, B. M. Neale, F. A. O'Neill, M. J. Owen, M. P. Milovancevic, D.<br>948 Dosthuma, J. Powell, A. L. Richards, B. P. Riley, D. Ruderfer, D. Rujescu, E. Sigurdsson, T. Silagadze, A.<br>949 B. Smit, H 947 Morris, O. Mors, P. B. Mortensen, B. M. Neale, F. A. O'Neill, M. J. Owen, M. P. Milovancevic, D.<br>948 Posthuma, J. Powell, A. L. Richards, B. P. Riley, D. Ruderfer, D. Rujescu, E. Sigurdsson, T. Silaga<br>950 B. Smit, H. S
- 949 B. Smit, H. Stefansson, S. Steinberg, J. Suvisaari, S. Tosato, M. Verhage, J. T. Walters, C. Multicenter<br>950 Genetic Studies of Schizophrenia, D. F. Levinson, P. V. Gejman, K. S. Kendler, C. Laurent, B. J. Mowry,<br>951 M 949 Genetic Studies of Schizophrenia, D. F. Levinson, P. V. Gejman, K. S. Kendler, C. Laurent, B. J. Mowry<br>951 M. C. O'Donovan, M. J. Owen, A. E. Pulver, B. P. Riley, S. G. Schwab, D. B. Wildenauer, F. Dudbridge,<br>952 Holma
- 
- 
- M. C. O'Donovan, M. J. Owen, A. E. Pulver, B. P. Riley, S. G. Schwab, D. B. Wildenauer, F. Dudbridge, P.<br>952 Holmans, J. Shi, M. Albus, M. Alexander, D. Campion, D. Cohen, D. Dikeos, J. Duan, P. Eichhammer, S.<br>953 Godard,
- 
- 
- 1952 Holmans, J. Shi, M. Albus, M. Alexander, D. Campion, D. Cohen, D. Dikeos, J. Duan, P. Eichhammer, S.<br>
1953 Godard, M. Hansen, F. B. Lerer, K. Y. Liang, W. Maier, J. Mallet, D. A. Nertney, G. Nestadt, N. Norton, F.<br>
19 Wormley, C. Psychosis Endophenotypes International, M. J. Arranz, S. Bakker, S. Bender, E. Bramon, D.<br>956 Collier, B. Crespo-Facorro, J. Hall, C. Iyegbe, A. Jablensky, R. S. Kahn, L. Kalaydjieva, S. Lawrie, C. M.<br>957 Lewis 954 — A. O'Neill, G. N. Papadimitriou, R. Ribble, A. R. Sanders, J. M. Silverman, D. Walsh, N. M. Williams, B.<br>955 — Wormley, C. Psychosis Endophenotypes International, M. J. Arranz, S. Bakker, S. Bender, E. Bramon,<br>956 — Collier, B. Crespo-Facorro, J. Hall, C. Iyegbe, A. Jablensky, R. S. Kahn, L. Kalaydjieva, S. Lawrie, C. M.<br>957 Lewis, K. Lin, D. H. Linszen, I. Mata, A. McIntosh, R. M. Murray, R. A. Ophoff, J. Powell, D. Rujescu, J.<br>958 V 1995 Collier, B. Crespo, M. Crespo, M. Crespo, M. Crespo, A. Golnoff, J. Powell, D. Rujescu, J.<br>1958 Collier, B. M. Walshe, M. Weisbrod, D. Wiersma, C. Wellcome Trust Case Control, P. Donnelly, I. Barros<br>1958 J. M. Blackwe
- 
- 958 Van Os, M. Walshe, M. Weisbrod, D. Wiersma, C. Wellcome Trust Case Control, P. Donnelly, I. Barrosis, J. M. Blackwell, E. Bramon, M. A. Brown, J. P. Casas, A. P. Corvin, P. Deloukas, A. Duncanson, J. Jankowski, H. S. M 959 J. M. Blackwell, E. Bramon, M. A. Brown, J. P. Casas, A. P. Corvin, P. Deloukas, A. Duncanson, J. Jankowski, H. S. Markus, C. G. Mathew, C. N. Palmer, R. Plomin, A. Rautanen, S. J. Sawcer, R. C. Trembath, A. C. Viswana Jankowski, H. S. Markus, C. G. Mathew, C. N. Palmer, R. Plomin, A. Rautanen, S. J. Sawcer, R. C.<br>961 Trembath, A. C. Viswanathan, N. W. Wood, C. C. Spencer, G. Band, C. Bellenguez, C. Freeman, (<br>962 Hellenthal, E. Giannoul
- Frembath, A. C. Viswanathan, N. W. Wood, C. C. Spencer, G. Band, C. Bellenguez, C. Freeman, G. Hellenthal, E. Giannoulatou, M. Pirinen, R. D. Pearson, A. Strange, Z. Su, D. Vukcevic, P. Donnell<br>1962 Langford, S. E. Hunt, S
- 
- 
- 
- 
- 1962 Hellenthal, E. Giannoulatou, M. Pirinen, R. D. Pearson, A. Strange, Z. Su, D. Vukcevic, P. Donnelly, Langford, S. E. Hunt, S. Edkins, R. Gwilliam, H. Blackburn, S. J. Bumpstead, S. Dronov, M. Gillman, Gray, N. Hammond 1962 Hellenthal, E. Giannoulatou, M. Pirinen, R. D. Pearson, A. Strange, Z. Su, D. Vukcevic, P. Donnelly, C.<br>
1963 Langford, S. E. Hunt, S. Edkins, R. Gwilliam, H. Blackburn, S. J. Bumpstead, S. Dronov, M. Gillman, E.<br>
196 964 Gray, N. Hammond, A. Jayakumar, O. T. McCann, J. Liddle, S. C. Potter, R. Ravindrarajah, M. Ricketts<br>965 A. Tashakkori-Ghanbaria, M. J. Waller, P. Weston, S. Widaa, P. Whittaker, I. Barroso, P. Deloukas, C. (<br>966 Mathe 965 A. Tashakkori-Ghanbaria, M. J. Waller, P. Weston, S. Widaa, P. Whittaker, I. Barroso, P. Deloukas, C. G<br>966 Mathew, J. M. Blackwell, M. A. Brown, A. P. Corvin, M. I. McCarthy, C. C. Spencer, E. Bramon, A. P.<br>967 Corvin 966 Mathew, J. M. Blackwell, M. A. Brown, A. P. Corvin, M. I. McCarthy, C. C. Spencer, E. Bramon, A. P. Corvin, M. C. O'Donovan, K. Stefansson, E. Scolnick, S. Purcell, S. A. McCarroll, P. Sklar, C. M. Hultman and P. F. Su
- 
- 
- 967 Corvin, M. C. O'Donovan, K. Stefansson, E. Scolnick, S. Purcell, S. A. McCarroll, P. Sklar, C. M. Hultman<br>968 and P. F. Sullivan (2013). "Genome-wide association analysis identifies 13 new risk loci for<br>969 schizophren 967 Corvin, M. C. O'Donovan, K. Stefansson, E. Scolnick, S. Purcell, S. A. McCarroll, P. Sklar, C. M. Hultman<br>968 and P. F. Sullivan (2013). "Genome-wide association analysis identifies 13 new risk loci for<br>969 schizophren 971 Ruden, J. B., L. L. Dugan and C. Konradi (2021). "Parvalbumin interneuron vulnerability and brain<br>1972 disorders." <u>Neuropsychopharmacology</u> 46(2): 279-287.<br>1974 Sanderson, D. J., M. A. Good, K. Skelton, R. Sprengel, P 970<br>971 Ruden, J. B., L. L. Dugan and C. Konradi (2021<br>972 disorders." <u>Neuropsychopharmacology</u> 46(2):<br>973 Sanderson, D. J., M. A. Good, K. Skelton, R. S<sub>l</sub><br>975 Bannerman (2009). "Enhanced long-term and 970 972 Ruden, J. B., L. Dugan and Enterneur (2012). Perical entertainment entertainty and brain<br>1973 Sanderson, D. J., M. A. Good, K. Skelton, R. Sprengel, P. H. Seeburg, J. N. Rawlins and D. M.<br>1974 Sanderson, D. J., M. A. G
- 
- 973
- 972 disorders. <u>Neuropsychopharmacology</u> 40(2): 279-287.<br>973 Sanderson, D. J., M. A. Good, K. Skelton, R. Sprengel, P<br>975 Bannerman (2009). "Enhanced long-term and impaired 975 Bannerman (2009). "Enhanced long-term and impaired short-term spatial memory in GluA1<br>975 Bannerman (2009). "Enhanced long-term and impaired short-term spatial memory in GluA1  $\langle 200\rangle$  Banderman (2009). "Enhanced long-term and impaired short-term spatial memory in GluAn American

970 Feceptor subunit knockout mice: evidence for a dual-process memory model." <u>Learn went</u> 10(0): 3/9-<br>978 Sanderson, D. J., R. Sprengel, P. H. Seeburg and D. M. Bannerman (2011). "Deletion of the GluA1 AMI<br>980 Feceptor s 977 386. 978<br>979 980 receptor subunit alters the expression of short-term memory." <u>Learn Mem</u> 18(3): 128-131.<br>981<br>982 Sans, N., C. Racca, R. S. Petralia, Y. X. Wang, J. McCallum and R. J. Wenthold (2001). "Synapse-<br>983 associated protein 981<br>981 Sans, N., C. Racca, R. S. Petralia, Y. X. Wang, J. McCallum and R. J. Wenthold (2001). "Syna<br>983 associated protein 97 selectively associates with a subset of AMPA receptors early in their<br>984 pathway." <u>J Neurosci</u> 981<br>982 983<br>983 associated protein 97 selectively associates with a subset of AMPA receptors early in their biosy<br>984 pathway." <u>J Neurosci</u> 21(19): 7506-7516.<br>985 Schizophrenia Working Group of the Psychiatric Genomics, C. (2014) 984 both protein 97 selectively associated protein 1992.<br>1985 Schizophrenia Working Group of the Psychiatric Genomics, C. (2014). "Biological insights from 108<br>1987 Schizophrenia-associated genetic loci." <u>Nature</u> 511(7510 984 pathway." <u>J Neurosci</u> 21(19): 7506-7516.<br>985 Schizophrenia Working Group of the Psychiatric Genomics, C. (2014). "Biological insights from 108<br>987 schizophrenia-associated genetic loci." <u>Nature</u> 511(7510): 421-427.<br>9 985 987 Schizophrenia Arching Order Inc." <u>Nature</u> 511(7510): 421-427.<br>988 Schwenk, J., D. Baehrens, A. Haupt, W. Bildl, S. Boudkkazi, J. Roeper, B. Fakler and U. Schulte (2011).<br>990 "Regional diversity and developmental dynam 988<br>988 Schwenk, J., D. Baehrens, A. Haupt, W. Bildl, S. Boudkkazi, J. Roep<br>990 "Regional diversity and developmental dynamics of the AMPA-rece<br>991 brain." <u>Neuron</u> 84(1): 41-54.<br>992 Shen, L., F. Liang, L. D. Walensky and 988 990 Fregional diversity and developmental dynamics of the AMPA-receptor proteome in the mammalian<br>991 Fregional diversity and developmental dynamics of the AMPA-receptor proteome in the mammalian<br>992 Shen, L., F. Liang, L. 991 Marin Martin 2018, 2018 of the Amples of the AMPA-receptor and the Mammalian<br>992 Shen, L., F. Liang, L. D. Walensky and R. L. Huganir (2000). "Regulation of AMPA receptor GluR1<br>994 Shen, L., F. Liang, L. D. Walensky an 991 brain." Neuron 84(1): 41-54. 992 994<br>994 subunit surface expression by a 4. 1N-linked actin cytoskeletal association." <u>J Neurosci</u> 20(21): 79:<br>995 7940.<br>997 Shi, S., Y. Hayashi, J. A. Esteban and R. Malinow (2001). "Subunit-specific rules governing AMPA<br> 995 7940.<br>995 7940.<br>996 Shi, S., Y. Hayashi, J. A. Esteban and R. Malinow (2001). "Subunit-specific rules governing AMPA<br>998 receptor trafficking to synapses in hippocampal pyramidal neurons." <u>Cell</u> 105(3): 331-343.<br>999 S 995 7940. 996<br>997 998 Feceptor trafficking to synapses in hippocampal pyramidal neurons." <u>Cell</u> 105(3): 331-343.<br>999<br>000 Stockwell, I., J. F. Watson and I. H. Greger (2024). "Tuning synaptic strength by regulation of AMI<br>001 glutamate rece 999<br>999 Stockwell, I., J. F. Watson and I. H. Greger (2024). "Tuning synaptic strength by regulation<br>001 glutamate receptor localization." <u>Bioessays</u>: e2400006.<br>002 Tamminga, C. A., S. Southcott, C. Sacco, A. D. Wagner an 999<br>1000 1001 glutamate receptor localization." <u>Bioessays</u>: e2400006.<br>1002<br>1003 Tamminga, C. A., S. Southcott, C. Sacco, A. D. Wagner and S. Ghose (2012). "Glutamate dysfunction in<br>1004 hippocampus: relevance of dentate gyrus and 1002<br>
1002 Tamminga, C. A., S. Southcott, C. Sacco, A. D. Wagner<br>
1004 hippocampus: relevance of dentate gyrus and CA3 signa<br>
1005<br>
1006 Traunmuller, L., A. M. Gomez, T. M. Nguyen and P. Sch<br>
1007 specification by a highly 1002 1004 hippocampus: relevance of dentate gyrus and CA3 signaling." <u>Schizophr Bull</u> 38(5): 927-935.<br>1005 Traunmuller, L., A. M. Gomez, T. M. Nguyen and P. Scheiffele (2016). "Control of neuronal synapse<br>1007 specification by 1004<br>1005<br>1006 Traunmuller, L., A. M. Gomez, T. M. Nguyen and P. Scheiffele (2016). "Control of neuronal sy<br>1007 specification by a highly dedicated alternative splicing program." <u>Science</u> 352(6288): 982-98<br>1008 Vogel-Cie 1005 1007 specification by a highly dedicated alternative splicing program." <u>Science</u> 352(6288): 982-986.<br>1008 Vogel-Ciernia, A. and M. A. Wood (2014). "Examining object location and object recognition memo<br>1010 mice." <u>Curr P</u> 1007 specification by a highly dedicated alternative splicing program. <u>Science</u> 352(6288): 982-988.<br>1008 Vogel-Ciernia, A. and M. A. Wood (2014). "Examining object location and object recognition m<br>1010 mice." <u>Curr Proto</u> 1008<br>1009 1010 mice." <u>Curr Protoc Neurosci</u> 69: 8 31 31-17.<br>1011 Voltson, J. F., A. Pinggera, H. Ho and I. H. Greger (2021). "AMPA receptor anchoring at CA1 synapses is<br>1013 determined by N-terminal domain and TARP gamma8 interacti 1010 mice. <u>Curr Futude Neurosci</u> 69: 8 31 31-17.<br>1011 Watson, J. F., A. Pinggera, H. Ho and I. H. G<br>1013 determined by N-terminal domain and TAF<br>1014 Yonezawa, K., H. Tani, S. Nakajima, N. Nag<br>1016 Uchida (2022). "AMPA re 1012 1013 determined by N-terminal domain and TARP gamma8 interactions." Nat Commun 12(1): 5083.<br>1014 Yonezawa, K., H. Tani, S. Nakajima, N. Nagai, T. Koizumi, T. Miyazaki, M. Mimura, T. Takahashi and H.<br>1016 Uchida (2022). "AM 1013 determined by N-terminal domain and TART gamma8 interactions. <u>Nat Commun 12(1): 5</u>003.<br>1014 Yonezawa, K., H. Tani, S. Nakajima, N. Nagai, T. Koizumi, T. Miyazaki, M. Mimura, T. Takahash<br>1016 Uchida (2022). "AMPA rece 1015 1016 Uchida (2022). "AMPA receptors in schizophrenia: A systematic review of postmortem studies on<br>1017 receptor subunit expression and binding." <u>Schizophr Res</u> 243: 98-109.<br>1018 Zamanillo, D., R. Sprengel, O. Hvalby, V. 1017 receptor subunit expression and binding." <u>Schizophr Res</u> 243: 98-109.<br>1018 Zamanillo, D., R. Sprengel, O. Hvalby, V. Jensen, N. Burnashev, A. Rozov, K. M. Kaiser, H. J. Koste<br>1020 Borchardt, P. Worley, J. Lubke, M. F 1017 receptor subunit expression and binding. <u>Schizophi Kes</u> 243: 90-109.<br>1018 Zamanillo, D., R. Sprengel, O. Hvalby, V. Jensen, N. Burnashev, A. Roz<br>1020 Borchardt, P. Worley, J. Lubke, M. Frotscher, P. H. Kelly, B. Somm 1018<br>1019 1020 Borchardt, P. Worley, J. Lubke, M. Frotscher, P. H. Kelly, B. Sommer, P. Andersen, P. H. Seeburg and B.<br>1021 Sakmann (1999). "Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial<br>1022 l Sakmann (1999). "Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial 1022 Iearning." <u>Science</u> 284(5421): 1805-1811.<br>1023<br>1023 1022 learning. <u>Science</u> 204(5421): 1805-1811.<br>1023

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- 2014 Zamanillo D.; Sprengel, R. H., Ø.; Jensen, V.; Burnashev, N.; Rozov, A.; and K. M. M. K. Kaiser, H. J.;<br>1025 Borchardt,T.; Worley, P.; Lubke, J.; Frotscher, M.; Kelly, P. H.; Sommer, B.; Andersen,P.; Seeburg. P. H.;<br>1
- Sakmann, B. (1999). "Importance of AMPA Receptors for Hippocampal Synaptic Plasticity But Not for 1027 Spatial<br>1026 Spatial<br>1028 Learning." <u>Science</u> 284.
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- 1028 Learnin<br>1028 Learnin<br>1029 1028 Learning. <u>Science</u> 204.<br>1029
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### $\mathsf F$   $_{\sf Training}$   $_{\sf WT}$   $_{\sf ACTD\,GluA1}$   $\mathsf G$   $_{\sf c.}$   $_{\sf n.S.}$   $_{\sf ***}$   $\mathsf H$   $_{\sf Training}$   $_{\sf wr}$   $_{\sf ACTD\,GluA1}$   $\mathsf I$ *Training* WT **ACTD GluA1** Training wT ∆CTD GluA1 ● n.s. **\*\*\* ロ** Training wT ∆CTD GluA1 **Ⅰ 。 \*\*\* \*\*\*** \*\*\* n.s. **\*\*\*** 80  $60 -$ Training Training Discrimination index Discrimination index 40 20 24 h 24 h  $\mathbf{0}$ novel novel -20 *Test Test*

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### Contextual fear conditioning test

WT **ACTD GluA1** 

