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Expression of activity-regulated transcripts in pyramidal neurons across the cortical visuospatial working memory network in unaffected comparison individuals and individuals with schizophrenia

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ABSTRACT

Visuospatial working memory (vsWM), which is impaired in schizophrenia (SZ), is mediated by multiple cortical regions including the primary (V1) and association (V2) visual, posterior parietal (PPC) and dorsolateral prefrontal (DLPFC) cortices. In these regions, parvalbumin (PV) or somatostatin (SST) GABA neurons are altered in SZ as reflected in lower levels of activity-regulated transcripts. As PV and SST neurons receive excitatory inputs from neighboring pyramidal neurons, we hypothesized that levels of activity-regulated transcripts are also lower in pyramidal neurons in these regions. Thus, we quantified levels of four activity-regulated, pyramidal neuron-selective transcripts, namely adenylate cyclase-activating polypeptide-1 (ADCYAP1), brain-derived neurotrophic factor (BDNF), neuronal pentraxin-2 (NPTX2) and neuritin-1 (NRN1) mRNAs, in V1, V2, PPC and DLPFC from unaffected comparison and SZ individuals. In SZ, BDNF and NPTX2 mRNA levels were lower across all four regions, whereas ADCYAP1 and NRN1 mRNA levels were lower in V1 and V2. The regional pattern of deficits in BDNF and NPTX2 mRNAs was similar to that in transcripts in PV and SST neurons in SZ. These findings suggest that lower activity of pyramidal neurons expressing BDNF and/or NPTX2 mRNAs might contribute to alterations in PV and SST neurons across the vsWM network in SZ.

Introduction

In schizophrenia (SZ), deficits in working memory (WM) have been suggested to be central to impairments in a range of cognitive functions (Silver et al., 2003; Barch and Ceaser, 2012) and thus key to one of the most debilitating symptom domains in the illness (Kahn and Keefe, 2013). Visuospatial WM (vsWM), which is impaired in SZ (Park and Holzman, 1992; Forbes et al., 2009; Matthews et al., 2014), depends on information flow across multiple cortical regions including the primary visual cortex (V1), association visual cortex (V2), posterior parietal cortex (PPC) and dorsolateral prefrontal cortex (DLPFC) (Linden, 2007; Christophel et al., 2017).

Information flow across these regions of the vsWM network is mediated by the axonal projections of excitatory pyramidal neurons that also provide excitatory inputs to local GABA neurons (Melchitzky and Lewis, 2003; Jiang et al., 2015), which, in turn, shape the activity of pyramidal neurons (Rao et al., 2000; Constantinidis et al., 2002). In each of these regions, levels of transcripts expressed in the parvalbumin (PV) or somatostatin (SST) subtypes of cortical GABA neurons were lower in individuals with SZ compared with unaffected comparison (UC) individuals (Tsubomoto et al., 2019), suggesting that alterations in both PV and SST neurons represent a shared feature across cortical regions of

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the vsWM network in SZ. Interestingly, some transcripts with lower levels in PV and SST neurons (e.g., PV, SST and GAD67 mRNAs) from SZ individuals are regulated by neuronal activity (Lau and Murthy, 2012; Cohen et al., 2016; Ampofo et al., 2020). Given that both PV and SST neurons receive direct excitatory inputs from neighboring pyramidal neurons (Melchitzky and Lewis, 2003; Jiang et al., 2015; Campagnola et al., 2022), we hypothesized that levels of activity-regulated transcripts are also lower in pyramidal neurons in SZ across regions of the vsWM network in a manner that is similar to the cross-regional alteration pattern of activity-regulated transcripts in PV and SST neurons.

To test this hypothesis, we used quantitative polymerase chain reaction (qPCR) to evaluate expression levels of activity-regulated, pyramidal neuron-selective transcripts in the total gray matter across four regions of the cortical vsWM network from 20 matched pairs of UC and SZ individuals. Specifically, we evaluated adenylate cyclase-activating polypeptide-1 (ADCYAP1), brain-derived neurotrophic factor (BDNF), neuronal pentraxin-2 (NPTX2) and neuritin-1 (NRN1) mRNAs. These transcripts are likely to be particularly informative as they are selectively expressed in pyramidal neurons in the human neocortex (Hodge et al., 2019; Ma et al., 2022) in a neuronal activity-regulated manner (Ataman et al., 2016; Mardinly et al., 2016; Hrvatin et al., 2018) and their protein products regulate the development and maintenance of synaptic connections, including those of GABA neurons (Kohara et al., 2007; Chang et al., 2010; Fujino et al., 2011; Picard et al., 2014; Varodayan et al., 2020; Martelle et al., 2021). Furthermore, a recent single-cell, spatial transcriptome study in the monkey neocortex demonstrated that these transcripts are expressed in different sets of excitatory neuron subtypes (Chen et al., 2023).

In addition, to determine if the regional expression patterns observed in total gray matter reflect those present in pyramidal neurons, we also analyzed previously published RNA sequencing (RNAseq) data of pools of layer 3 pyramidal neurons captured from V1, PPC and DLPFC of 39 UC individuals (Enwright et al., 2022). Layer 3 pyramidal neurons appear to have critical roles in WM because 1) across cortical regions of vsWM network these neurons exhibit activities that represent specific information during vsWM tasks (Goldman-Rakic, 1995; Chafee and Goldman-Rakic, 1998; van Kerkoerle et al., 2017) and 2) these neurons, through their corticocortical axonal projections (Jones, 1984; Lewis and Gonzalez-Burgos, 2000), directly mediate information flow across cortical regions of the vsWM network (Felleman and Van Essen, 1991; Arion et al., 2023). Furthermore, they are the major source of excitatory inputs to neighboring PV and SST neurons via local axon collaterals (Melchitzky and Lewis, 2003; Jiang et al., 2015; Campagnola et al., 2022).

Methods

2.1. Human individuals

Brain specimens ($N = 40$) were obtained, following consent from the next of kin, during autopsies conducted at the Allegheny County (Pittsburgh, PA; $N = 37$) or the Davidson County (Nashville, TN; $N = 3$) Medical Examiner's Office. An independent committee of clinicians made consensus, lifetime DSM-IV diagnoses for each individual using the results of an expanded psychological autopsy, including structured interviews with family members and review of medical records, as well as toxicology and neuropathology reports (J.R. Glausier et al., 2020). The same approach was used to confirm the absence of lifetime psychiatric and neurologic disorders in the UC individuals. All procedures were approved by the University of Pittsburgh Committee for Oversight of Research and Clinical Training Involving Decedents and Institutional Review Board for Biomedical Research, as well as by the Ethics Committees of Kanazawa University Graduate School of Medical Sciences and Nara Medical University.

To reduce biological variance between groups, and to employ a design that controlled for experimental variance, each individual with SZ was matched to one UC individual for sex, and as closely as possible for age (Table 1, Supplementary Table 1). Mean age, body mass index (BMI), postmortem interval (PMI), brain pH, RNA integrity number (RIN) and storage time at −80 °C did not differ significantly between the two groups, nor did race distribution (Table 1).

2.2. Tissue preparation

The right hemisphere of each brain was blocked coronally, immediately frozen and stored at −80 °C. The gray matter tissues were dissected from each of the four cortical regions (V1, V2, PPC and DLPFC) as described previously (Hoftman et al., 2018) (Supplementary Methods, Supplementary Figure 1) and homogenized in TRIzol reagent (Invitrogen, Carlsbad, CA).

2.3. qPCR procedures

Total RNA was isolated from the homogenate samples and converted into cDNA as described previously (Tsubomoto et al., 2019) (Supplementary Methods). Real-time amplification of ADCYAP1, BDNF, NPTX2, and NRN1 mRNAs, as well as three internal control transcripts [beta-actin (ACTB), glyceraldehyde-3-phosphate (GAPDH) and peptidylprolyl isomerase A (PPIA)] were performed as described previously (Vandesompele et al., 2002; Tsubomoto et al., 2019) (Supplementary Methods), using forward and reverse primers designed to amplify fragments of 87 to 127 bp in the regions common to all variants with amplification efficiency ≥ 96 % (Supplementary Table 2). The primer set for BDNF mRNA was designed to avoid the region included in the non-coding antisense RNA (BDNF-AS).

The expression levels of the target transcripts were determined as expression ratios to the geometric mean of internal control transcripts as described previously (Tsubomoto et al. 2019) (Supplementary Methods). The mean expression levels of internal control transcripts did

Table 1
Summary of demographic and postmortem characteristics of human individuals.

Measure	Unaffected Comparison ($n = 20$)		Schizophrenia ($n = 20$)		Statistics
	Male	**Female**	**Male**	**Female**	
Sex	14	6	14	6	(N/A)
	White	**Black**	**White**	**Black**	
Race	15	5	14	6	$\chi^2 = 0.13$; $p = 0.72$
	Mean	**SD**	**Mean**	**SD**	
Age (years)	45.4	11.6	44.3	10.4	$t_{1,38} = 0.33$; $p = 0.74$
BMI	31.3	7.2	28.9	7.3	$t_{1,36} = 1.0$; $p = 0.32$
PMI (hours)	15.3	5.8	14.2	6.4	$t_{1,38} = 0.59$; $p = 0.56$
Brain pH	6.6	0.2	6.5	0.3	$t_{1,38} = 2.0$; $p = 0.05$
RIN	8.4	0.5	8.3	0.6	$t_{1,38} = 0.44$; $p = 0.66$
Tissue StorageTime (months)	196.5	39.9	197.7	47.3	$t_{1,38} = -0.08$; $p = 0.94$

N/A, not applicable; BMI, body mass index; PMI, postmortem interval; RIN, RNA integrity number.

not differ significantly by diagnosis ($F_{1,38} = 1.92$, $p = 0.174$) and the diagnosis-by-region interaction was not significant ($F_{3,114} = 0.31$, $p = 0.817$). We did detect a significant effect of region ($F_{3,114} = 8.00$, $p < 0.001$), with post hoc comparisons revealing a significant difference between V1 and DLPFC. However, this difference appears to have a limited effect on the comparison of target transcript levels between V1 and DLPFC as it is smaller in size (< 2.1 %) relative to the size of observed differences in target transcripts (all > 13.4 %). Cases with transcript levels more than 3 SDs from the mean of all individuals in any region were considered as outliers for that measure and pairs including such cases were removed from the comparison between UC and SZ individuals.

2.4. qPCR data analysis

Analyses were performed with R version 4.1.3 (R: The R Project for Statistical Computing; http://www.r-project.org) using the "lme4", "lmerTest", "tidyverse" and "emmeans" packages. To assess transcript levels across the four regions, a linear mixed model (LMM) was performed with observations from the four regions in each individual as repeated measures to account for within-individual correlation among four regions. To compare transcript levels across the four regions in UC individuals, the LMM included transcript level as the dependent variable, region as a fixed effect, individual as a random effect, and sex, age, PMI, brain pH, RIN and tissue storage time as covariates. F-tests were used to assess the overall effect of region. If region effect was significant, post hoc pairwise comparisons between regions were performed by Tukey's test. To determine if the expression of these transcripts was altered in SZ across regions, the LMM was performed with transcript level as the dependent variable, diagnosis, region and diagnosis-by-region interaction as the fixed effects, individual as a random effect, and the same set of covariates. F-tests were used to test the diagnosis and diagnosis-by-region interaction effects. If the diagnosis-by-region interaction was significant, post hoc pairwise comparisons were performed to assess the diagnosis effect in each region via Tukey's test. In each region, the magnitudes of transcript changes in SZ relative to UC individuals are presented as percentage differences as well as Cohen's d effect sizes (Cohen, 1988). Negative Cohen's d values indicate that mean transcript levels are lower in SZ relative to UC individuals.

To compare alterations in the activity-regulated transcripts with previously reported deficits in transcripts from PV and SST neurons (PV, SST and GAD67 mRNAs) (Tsubomoto et al., 2019) across the regions, composite scores were computed for three groups of transcripts (ADCYAP1 and NRN1 mRNAs, BDNF and NPTX2 mRNAs, and PV, SST and GAD67 mRNAs) as the means of Z-scored expression levels of transcripts belonging to each group (Supplementary Methods). Transcript levels of PV, SST and GAD67 mRNAs were obtained from the previously published analysis of the same cohort used in this study (Tsubomoto et al., 2019). In each region, the magnitudes of diagnosis effect on composite scores are presented as Cohen's d with 95 % confidence intervals (CI) (Nakagawa and Cuthill, 2007).

The potential effects of certain cooccurring factors, such as the use of prescription drugs (benzodiazepines and/or anticonvulsants, antidepressants and antipsychotics) at time of death (ATOD), tobacco use ATOD, and suicide as the manner of death, on each target transcript were tested by the LMM with transcript level as the dependent variable, cooccurring factor, region and cooccurring factor-by-region interaction as the fixed effects, individual as a random effect, and sex, age, PMI, RIN, tissue storage time and brain pH as covariates. For each transcript, p values were corrected for multiple comparisons for 5 cooccurring factors using the Benjamini-Hochberg Method with the false discovery rate of 5 %.

All LMM analyses of individual target transcripts were conducted on log-transformed data and only significant covariates were included in the final reported results.

2.5. Analysis of RNAseq data from pools of layer 3 pyramidal neurons

We also examined the transcripts of interest in a previously published RNAseq data set obtained from pools of 100 individually-dissected layer 3 pyramidal neurons collected from V1, PPC and DLPFC of 39 UC individuals (Enwright et al., 2022) (for demographic information see Enwright et al. 2022). Among these 39 UC individuals, 19 UC individuals were common to the 20 UC individuals analyzed in the current qPCR analysis. To compare RNAseq data for each transcript across V1, PPC and DLPFC from UC individuals, the LMM included transcript level as the dependent variable, region as a fixed effect, individual as a random effect, and sex, age, PMI, brain pH and RIN as covariates, with only significant covariates included in the final reported results. If the region effect was significant, post hoc pairwise comparisons between regions were performed by Tukey's test.

2.6. Analysis of microarray data of isolated pyramidal neurons from DLPFC of antipsychotic-exposed monkeys

Levels of ADCYAP1, BDNF, NPTX2 and NRN1 mRNAs were obtained from microarray data of pools of individually captured pyramidal neurons from DLPFC layers 3 and 5 of monkeys chronically exposed to haloperidol, olanzapine or placebo ($n = 6$ per group) (Dorph-Petersen et al., 2004). Levels of the transcripts of interest were computed as described previously (Datta et al., 2015) and used as the dependent variable in an analysis of variance model that assessed the effect of antipsychotic-exposure on each transcript.

3. Results

3.1. Levels of activity-regulated, pyramidal neuron-selective transcripts across regions of vsWM network in UC individuals

In UC individuals, the levels in total gray matter of pyramidal neuron-selective, activity-regulated transcripts showed two patterns of regional differences across the vsWM network (Fig. 1). In the first pattern, transcript levels for ADCYAP1 ($F_{3,57} = 17.38$, $p < 0.001$), BDNF ($F_{3,57} = 33.98$, $p < 0.001$) and NPTX2 ($F_{3,57} = 54.73$, $p < 0.001$) increased from posterior to anterior regions. Specifically, levels of these three transcripts were lowest in V1, intermediate in V2 and highest in PPC and DLPFC (Fig. 1A-C). In contrast, NRN1 mRNA ($F_{3,57} = 8.68$, $p < 0.001$) showed the opposite pattern with levels highest in V1 and decreasing across the vsWM network (Fig. 1D), although the magnitude of the between-region differences appears smaller than for transcripts in the first pattern. Among 20 UC individuals, the numbers of individuals with higher ADCYAP1, BDNF and NPTX2 mRNA levels in DLPFC than in V1 were 20, 20 and 19, respectively, whereas the number of individuals with higher NRN1 mRNA levels in V1 than in DLPFC was 16.

We also evaluated the levels of these transcripts in isolated layer 3 pyramidal neurons from V1, PPC and DLPFC of UC individuals using our previously published RNAseq data (Enwright et al., 2022). The effect of region was significant or nearly significant for ADCYAP1 ($F_{2,76} = 41.18$, $p < 0.001$), BDNF ($F_{2,76} = 2.80$, $p = 0.067$), and NPTX2 ($F_{2,76} = 104.62$, $p < 0.001$) mRNAs (Fig. 1E-G). Similar to the qPCR data of gray matter, ADCYAP1 and NPTX2 showed posterior-to-anterior increases with levels of these mRNAs significantly higher in DLPFC than in V1 (Fig. 1E, G). BDNF mRNA showed a similar trend with mean levels lowest in V1, intermediate in PPC and highest in DLPFC (Fig. 1F). In contrast to the qPCR data, NRN1 mRNA levels in layer 3 pyramidal neurons did not differ across vsWM regions ($F_{2,76} = 0.39$, $p = 0.678$) (Fig. 1H).

3.2. Effect of SZ on activity-regulated, pyramidal neuron-selective transcripts in regions of vsWM network

For ADCYAP1 mRNA, our mixed model detected a significant effect of diagnosis ($F_{1,38} = 6.87$, $p = 0.013$), significant effects of region ($F_{3,114}$

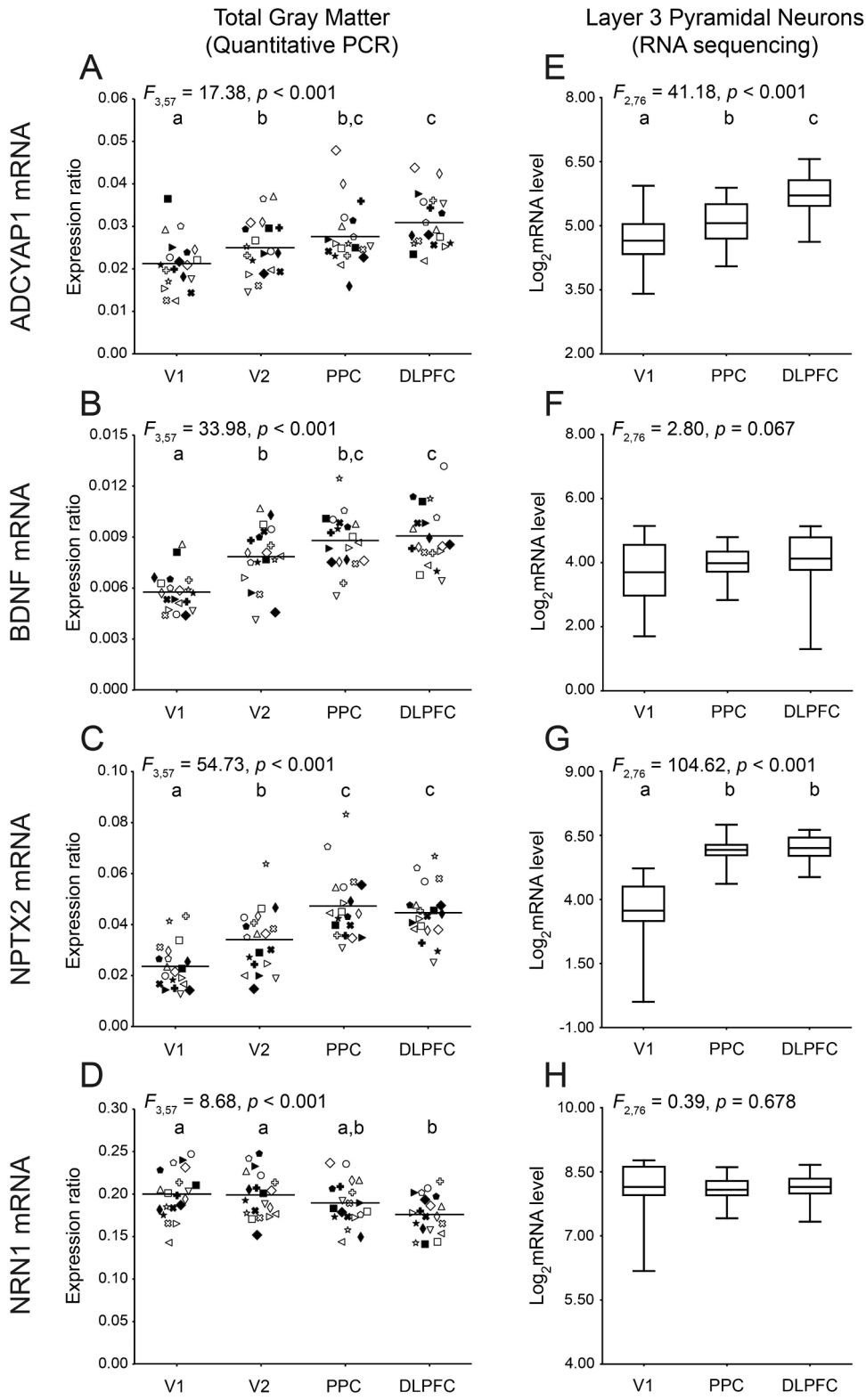

Fig. 1. Expression levels of activity-regulated, pyramidal neuron-selective transcripts across the four regions of the cortical visuospatial working memory network in unaffected comparison (UC) individuals measured in total gray matter by quantitative polymerase chain reaction (qPCR) (A-D) and in layer 3 pyramidal neurons by RNA sequencing (RNAseq) (E-H). The linear mixed model results are shown at the top left of each panel for each transcript. Within each panel, symbols indicate individuals and horizontal bars represent group means. For each transcript, regions that do not share the same lower-case letter are significantly different by post hoc Tukey's tests with alpha level of 0.05. For qPCR results (A-D), transcript levels of each UC individual are shown by the same symbol across all regions and graphs. For RNAseq results (E-H), box plots depict the mean, and 25th and 75th percentiles, with whiskers extending to the 95th percentiles of each distribution. V1, primary visual cortex; V2, association visual cortex; PPC, posterior parietal cortex; DLPFC, dorsolateral prefrontal cortex.

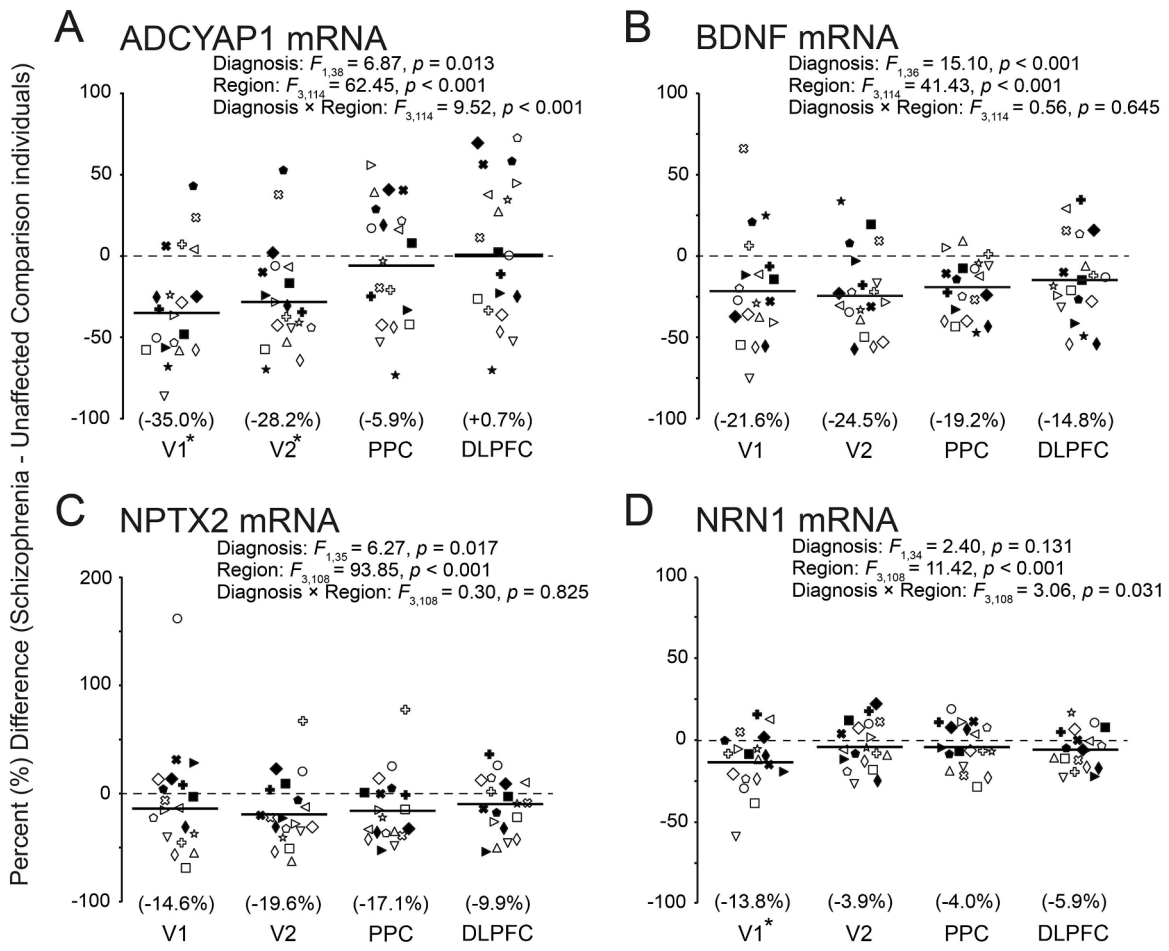

Fig. 2. Effect of schizophrenia (SZ) on activity-regulated, pyramidal neuron-selective transcripts across the four cortical regions of visuospatial working memory network. For each panel (A-D), transcript name is at the top left and the linear mixed model results at the top center. In each panel, symbols indicate the percentage difference between the unaffected comparison (UC) and SZ individual in each pair; symbols correspond to the UC individual plotted in Fig. 1 for a given pair. The percentage differences in mean levels between SZ and UC individuals are indicated by horizontal bars and shown in parentheses. Asterisks (*) indicate significant differences between UC and SZ individuals in each region by post hoc Tukey's tests that were performed when the linear mixed model detected a significant diagnosis-by-region interaction. V1, primary visual cortex; V2, association visual cortex; PPC, posterior parietal cortex; DLPFC, dorsolateral prefrontal cortex.

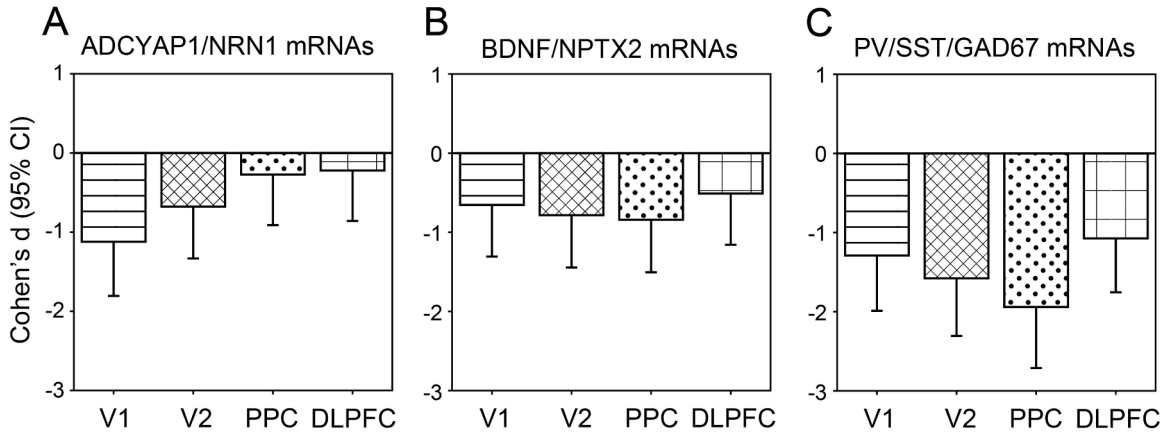

Fig. 3. Effect of schizophrenia (SZ) on composite scores obtained for activity-regulated, pyramidal neuron-selective transcripts and for transcripts in PV and SST neurons in each region of the cortical visuospatial working memory network. In each panel (A-C), bargraphs show the Cohen's d effect sizes of SZ on transcript composite scores across the regions for three groups of transcripts, ADCYAP1 and NRN1 mRNAs (A), BDNF and NPTX2 mRNAs (B) and PV, SST and GAD67 mRNAs (C). Error bars indicate 95 % confidence intervals (CI). V1, primary visual cortex; V2, association visual cortex; PPC, posterior parietal cortex; DLPFC, dorsolateral prefrontal cortex.

= 62.45, $p < 0.001$) and diagnosis-by-region interaction ($F_{3,114} = 9.52$, $p < 0.001$) (Fig. 2A). Compared with UC individuals, ADCYAP1 mRNA levels were significantly lower in V1 (Cohen's $d = -1.21$, $p < 0.001$) and V2 (Cohen's $d = -0.99$, $p = 0.002$) but unaltered in PPC and DLPFC of individuals with SZ. Levels of BDNF mRNA significantly differed by diagnosis ($F_{1,36} = 15.10$, $p < 0.001$) and by region ($F_{3,114} = 41.43$, $p < 0.001$), but the interaction term was not significant ($F_{3,114} = 0.56$, $p = 0.645$) (Fig. 2B). Compared with UC individuals, BDNF mRNA levels were lower in V1, V2, PPC and DLPFC (Cohen's $d = -0.80$, -1.03, -0.87 and -0.60, respectively) in SZ individuals. For NPTX2 mRNA levels, we detected a significant effect of diagnosis ($F_{1,35} = 6.27$, $p = 0.017$) and a significant effect of region ($F_{3,108} = 93.85$, $p < 0.001$), without a diagnosis-by-region interaction ($F_{3,108} = 0.30$, $p = 0.825$) (Fig. 2C). NPTX2 mRNA levels were lower in V1, V2, PPC and DLPFC (Cohen's $d = -0.37$, -0.51, -0.59, and -0.33, respectively) in individuals with SZ. Finally, NRN1 mRNA levels showed significant effects of region ($F_{3,108} = 11.42$, $p < 0.001$) and diagnosis-by-region interaction ($F_{3,108} = 3.06$, $p = 0.031$), but the effect of diagnosis was not significant ($F_{1,34} = 2.40$, $p = 0.131$) (Fig. 2D). NRN1 mRNA levels were significantly lower in V1 (Cohen's $d = -0.91$, $p = 0.005$), but unaltered in the other regions.

3.3. Comparison with transcript alterations in PV and SST neurons

The findings above reveal two distinct cross-regional patterns of activity-regulated transcript alterations in SZ: ADCYAP1 and NRN1 mRNAs levels were lower only in the two occipital regions (Fig. 2A and D), whereas the deficits in BDNF and NPTX2 mRNA levels were comparable across all four regions (Fig. 2B and C). Therefore, to assess the relationship of activity-regulated transcripts with the previously reported transcript alterations in PV and SST neurons in SZ, we computed composite scores in each region of each individual for ADCYAP1 and NRN1 mRNAs, for BDNF and NPTX2 mRNAs and for PV, SST and GAD67 mRNAs using previously published data from the same cohort (Tsubomoto et al., 2019). The magnitude (Cohen's d effect size) of the deficit in the ADCYAP1/NRN1 composite scores in SZ was largest in V1 and decreased from posterior to anterior regions (Fig. 3A). In contrast, although regional differences in the magnitudes of the disease effect were much smaller for the BDNF/NPTX2 scores, the magnitudes of deficits were in the order of PPC>V2>V1>DLPFC (Fig. 3B), the same regional order observed for the larger deficits in the PV/SST/GAD67 scores (Fig. 3C). Although the data points were limited to the four regions, the effects of SZ on BDNF/NPTX2 scores and PV/SST/GAD67 scores were positively correlated ($r = 0.96$, $p = 0.042$) across these regions, whereas the ADCYAP1/NRN1 and PV/SST/GAD67 scores were not ($r = -0.19$, $p = 0.890$).

3.4. Effects of cooccurring factors on activity-regulated transcripts in SZ individuals

In the LMM model, none of cooccurring factors, including the use of prescription drugs (benzodiazepines and/or anticonvulsants, antidepressants and antipsychotics) ATOD, tobacco use ATOD or suicide (all $p > 0.073$), nor the interaction between each of these factors and regions (all $p > 0.069$) exhibited a significant effect on levels of all transcripts in individuals with SZ (Supplementary Table 3), except for a significant effect of benzodiazepines/anticonvulsants ATOD on NRN1 mRNA levels (Supplementary Figure 2). Individuals with SZ who used benzodiazepines/anticonvulsants ATOD had NRN1 mRNA levels that were 16–29 % higher across regions compared with those who did not use these drugs (Supplementary Figure 2).

To further assess the effect of antipsychotics on the four transcripts, we analyzed microarray data of pooled pyramidal neurons individually captured from layers 3 and 5 of DLPFC of monkeys chronically exposed to haloperidol, olanzapine or placebo (Datta et al., 2015). The exposure to antipsychotics did not have a significant effect on any of the four transcripts in pyramidal neurons from layer 3 (all $F_{2,15} < 0.59$, all $p > 0.567$) or layer 5 (all $F_{2,15} < 1.14$, all $p > 0.345$).

4. Discussion

In this study, we quantified levels of four neuronal activity-regulated transcripts that are selectively expressed in pyramidal neurons across four cortical regions of vsWM network from 20 matched pairs of UC and SZ individuals. In UC individuals, levels of ADCYAP1, BDNF and NPTX2 mRNAs were lowest in V1 and increased from posterior to anterior regions with the highest levels in the PPC and DLPFC, whereas NRN1 mRNA levels were higher in V1 and V2 than in PPC or DLPFC. Relative to UC individuals, levels of BDNF and NPTX2 mRNAs were lower in SZ across all four regions, whereas ADCYAP1 and NRN1 mRNA levels were lower in V1 and V2, but not in PPC or DLPFC. Across the four regions, the deficits in BDNF and NPTX2 mRNA levels were similar to the previously reported deficits in PV, SST and GAD67 mRNA levels in the same cohort. These findings are consistent with the idea that the activity of pyramidal neurons that selectively express BDNF and/or NPTX2 mRNAs is lower in SZ and contribute to alterations in PV and SST neurons across multiple regions of the cortical vsWM network in SZ.

4.1. Transcript levels in UC individuals

Our qPCR findings revealed that levels of ADCYAP1, BDNF and NPTX2 mRNAs increased, whereas those of NRN1 mRNAs declined from posterior visual to anterior association regions of the vsWM network in UC individuals. As recent single-cell transcriptome analyses of the primate neocortex revealed that these transcripts are selectively expressed in different sets of excitatory neuron subtypes including those in layer 3 (Hodge et al., 2019; Ma et al., 2022; Chen et al., 2023), the cross-regional differences in their levels in total gray matter could reflect regional differences in the activity and/or abundance of pyramidal neuron subtypes that selectively express each of these transcripts. The qPCR result of ADCYAP1, BDNF and NPTX2 mRNAs were replicated in our RNAseq analysis of isolated layer 3 pyramidal neurons (Enwright et al., 2022), suggesting that regional differences in the mRNA levels in total gray matter reflect, at least in part, their expression in layer 3 pyramidal neurons. Interestingly, layer 3 pyramidal neurons exhibit progressive increases in the size and complexity of dendritic arbors (Elston and Rosa, 1997; Elston, 2000) and in the number and density of dendritic spines, the principal sites of excitatory synapses on pyramidal neurons (Spruston, 2008), from V1 to DLPFC (Elston, 2000; Elston et al., 2011). Furthermore, in monkeys, the magnitude, frequency and duration of excitatory synaptic inputs to layer 3 pyramidal neurons were all greater in DLPFC than in V1 (Amatrudo et al., 2012), indicating greater amounts and more effective summation of excitatory inputs to these neurons in DLPFC than in V1. Therefore, the posterior-to-anterior increase in ADCYAP1, BDNF and NPTX2 mRNAs might reflect the regional gradient in the activity of layer 3 pyramidal neurons. Consistent with this idea, in our RNAseq data of isolated layer 3 pyramidal neurons, levels of transcripts for oxidative phosphorylation, which reflect neuronal activity (Wong-Riley, 2012), exhibited higher expression levels in DLPFC and PPC than in V1 (Enwright et al., 2022).

In contrast, NRN1 mRNA levels were higher in V1 and V2 than in DLPFC with the levels in PPC intermediate by qPCR. However, the RNAseq analysis of isolated layer 3 pyramidal neurons did not detect a significant difference across the regions. The RNAseq data for 19 UC individuals, which are common to the current qPCR analysis, showed a trend of difference in NRN1 mRNA among the four regions ($F_{2,36} = 2.78$, $p = 0.075$) with the levels in V1 higher by 2.3 % than in DLPFC, whereas in the qPCR data for the total gray matter of the same 19 UC individuals NRN1 mRNA levels differ significantly across regions ($F_{3,54} = 8.21$, $p < 0.001$) with the levels in V1 significantly higher by 12.9 % than those in DLPFC. It is also possible that the observed difference between V1 and DLPFC in qPCR data is overrated by the lower mean levels of internal

control transcripts in V1 relative to DLPFC in UC individuals. However, this influence appears to be limited as the mean levels of the three control transcripts were lower by 2.1 % in V1 than in DLPFC, whereas NRN1 mRNA levels were higher by 13.5 % in V1 than in DLPFC. Together, these findings suggest that the posterior-to-anterior decline in NRN1 mRNA levels in total gray matter is not merely an artifact associated with the difference in cohorts or the regional difference in the levels of internal control transcripts. It is possible that the qPCR results reflect, at least in part, NRN1 mRNA expression in non-layer 3 pyramidal neurons. Interestingly, in a recent single-cell, spatial transcriptome analysis of the monkey cortex (Chen et al., 2023), NRN1 mRNA was selectively detected in seven excitatory neuron subtypes that exhibited gradual decreases in the density from posterior visual to anterior association regions along the hierarchy of visual cortices. Among these subtypes, six subtypes, which represent the majority in the total densities of the seven subtypes across these regions, were located outside of layer 3. Therefore, the posterior-to-anterior decline of NRN1 mRNA levels might reflect the regional gradients of the density of the pyramidal neuron subtypes located outside of layer 3.

4.2. Alterations in SZ individuals

We have previously demonstrated that levels of BDNF and NPTX2 mRNAs were lower in the DLPFC of SZ individuals (Hashimoto et al., 2005; Kimoto et al., 2015). In the current study, we detected significant effects of diagnosis on BDNF and NPTX2 mRNAs, respectively, without a significant diagnosis-by-region interaction, indicating that these transcripts are similarly lower across the four regions in SZ individuals. As both BDNF and NPTX2 are synthesized in pyramidal neurons in an activity-dependent manner (Tsui et al., 1996; Hrvatin et al., 2018; Esvald et al., 2022), their lower levels in SZ could reflect reduced activity of pyramidal neurons, which could contribute to lower levels of activity-regulated transcripts in PV and SST neurons via excitatory inputs from pyramidal neurons. Furthermore, BDNF has been reported to be necessary for the formation and maintenance of inhibitory synapses by cortical GABA neurons (Kohara et al., 2007) and was shown to regulate expression of PV (Huang et al., 1999; Sakata et al., 2009), SST (Glorioso et al., 2006; Mellios et al., 2009) and GAD67 (Matsumoto et al., 2006; Hanno-Iijima et al., 2015). NPTX2 is released from pyramidal neurons, accumulates at excitatory synapses on PV neurons and enhances excitatory inputs to these neurons by recruiting AMPA receptors to synaptic surface (Chang et al., 2010). Therefore, lower levels of BDNF and NPTX2 mRNAs could represent, in addition to reduced excitatory inputs to PV and SST neurons, a direct molecular mechanism that could contribute to the lower transcript levels in PV and SST neurons across cortical regions.

In contrast to BDNF and NPTX2 mRNAs, levels of ADCYAP1 and NRN1 mRNAs were lower only in posterior visual regions. ADCYAP1 and NRN1 mRNAs are selectively expressed in pyramidal neurons of human cortex (Hodge et al., 2019; Ma et al., 2022) and upregulated with enhanced activity in pyramidal neurons in rodent cortex (Hrvatin et al., 2018). As recent single-nucleus transcriptome analyses revealed multiple pyramidal neuron subtypes in the primate neocortex (Hodge et al., 2019; Ma et al., 2022; Chen et al., 2023), the region-specific deficits in ADCYAP1 and NRN1 mRNAs could reflect that pyramidal neuron subtypes that selectively express these transcripts are hypoactive primarily in posterior regions in SZ individuals. Alternative, though not mutually exclusive, is the possibility that activity-dependent regulation of these transcripts in pyramidal neurons differs across cortical regions so that the effect of activity has greater impacts on these transcripts in posterior than in anterior regions. Activity-regulated transcription was shown to occur through the interaction with epigenetic mechanisms, such as DNA methylation and chromatin modifications (Yap and Greenberg, 2018; Pumo et al., 2022). Among different cell types in human neocortex, pyramidal neurons exhibited the greatest cross-regional variability in chromatin accessibility (Hauberg et al., 2020), and in monkeys, most pyramidal neuron subtypes that are defined by their layer localization and projection targets showed different chromatin accessibility patterns, especially in the gene regulatory regions, across different neocortical regions (Lei et al., 2022). Therefore, the lower levels of ADCYAP1 and NRN1 mRNAs in posterior visual, but not anterior association, regions might reflect regional differences in epigenetic regulation that could contribute to region-selective influence of pyramidal neuron activity on these transcripts.

The cross-regional patterns of deficits in SZ were different between BDNF and NPTX2 mRNAs and ADCYAP1 and NRN1 mRNAs and the pattern of transcript alterations in PV and SST neurons was similar to that of BDNF and NPTX2 mRNAs. In a recent single-cell, spatial transcriptome analysis of the monkey cortex (Chen et al., 2023), 59 out of 122 cortical excitatory neuron subtypes were found to express at least one of the four activity-regulated transcripts as their selective markers. Among them, 25 subtypes selectively express ADCYAP1 and/or NRN1 mRNAs without selective expression of BDNF or NPTX2 mRNAs and 19 subtypes selectively express BDNF and/or NPTX2 mRNAs without selective expression of ADCYAP1 or NRN1 mRNAs. These findings suggest that pyramidal neuron subtypes that selectively express BDNF and/or NPTX2 mRNAs contribute to alterations of PV and SST neurons through their lower activity and reduced synthesis of BDNF and NPTX2 in each region of vs WM network.

4.3. Evidence supporting lower pyramidal neuron activity in SZ

In SZ, the density of dendritic spines was found to be lower across multiple cortical regions (Glausier and Lewis, 2013). Given that spines are the site of most excitatory inputs to pyramidal neuron, these findings have been interpreted as evidence of lower excitatory drive to, and hence lower activity of, pyramidal neurons. This interpretation is supported by findings that markers of energy production are also lower in pyramidal neurons in cortical regions of the vsWM network in SZ (Arion et al., 2015; Glausier et al., 2020; Kimoto et al., 2022). Furthermore, many SZ risk loci identified by large-scale genetic studies implicate genes involved in synaptic glutamate signaling or spine formation and maintenance (Singh et al., 2022; Trubetskoy et al., 2022). Together, these findings converge on the idea that fewer excitatory inputs to cortical pyramidal neurons contribute to lower activity of these neurons in SZ. Previous functional imaging studies have shown lower activity of DLPFC and PPC during WM tasks (Minzenberg et al., 2009; Barch and Ceaser, 2012). As pyramidal neurons are excitatory and represent the majority of neurons across cortical regions (Hendry et al., 1987; Jorstad et al., 2023), these findings are also consistent with lower activity of pyramidal neurons in the vsWM network in SZ.

4.4. Effects of cooccurring factors

Several lines of evidence suggest that altered levels of activity-regulated transcripts in pyramidal neurons across the regions of vsWM network are unlikely to be the consequences of other factors frequently associated with SZ. First, our LMM model did not reveal a significant effect of cooccurring factors, such as prescription drug use ATOD (including benzodiazepines/anticonvulsants, antidepressants and antipsychotics), tobacco use ATOD or death by suicide, or a significant coocurring factor-by-region interaction for ADCYAP1, BDNF and NPTX2 mRNAs in SZ individuals (Supplementary Table 3). For NRN1, only use of benzodiazepines/anticonvulsants ATOD had a significant effect without a significant interaction with region. However, NRN1 mRNA levels were higher in SZ individuals treated with benzodiazepines/anticonvulsants ATOD than in those who were not treated with these drugs across the regions (Supplementary Figure 2). Therefore, benzodiazepines/anticonvulsants use ATOD did not explain the lower NRN1 mRNA levels in SZ compared to UC individuals. Second, our previous studies in the DLPFC of individuals with SZ demonstrated that BDNF mRNA levels did not differ as a function of antidepressant or antipsychotic use or of

death by suicide (Hashimoto et al., 2005), and NPTX2 mRNA levels were not affected by use of benzodiazepines/anticonvulsants, antidepressants or antipsychotics ATOD, tobacco use ATOD, or death by suicide (Kimoto et al., 2015). Third, neither BDNF nor NPTX2 mRNA levels were altered in the total gray matter of DLPFC of monkeys chronically exposed to antipsychotics (Hashimoto et al., 2005; Kimoto et al., 2015). Fourth, in the same antipsychotic-exposed monkeys, none of the four transcripts exhibited a significantly altered levels in pooled pyramidal neurons individually captured from layers 3 or 5 of the DLPFC. Finally, the comparable magnitudes of alterations of BDNF and NPTX2 mRNAs as well as posterior region-dominant alterations of ADCYAP1 and NRN1 mRNAs argue against the potential influence of antipsychotics because any effects of antipsychotics would likely to show a posterior-to-anterior increase that reflect greater densities of dopamine terminals (Lewis et al., 1987; Gaspar et al., 1989) and receptors (Lidow et al., 1989) in anterior than in posterior regions.

4.5. Conclusions

Our analyses of four activity-regulated transcripts that are selectively expressed in pyramidal neurons across the four cortical regions of vsWM network revealed two opposite cross-regional expression patterns in UC individuals, which appear to reflect regional differences in activity and/or relative abundance of pyramidal neuron subtypes selectively expressing each transcript. In SZ individuals, levels of these transcripts were lower across the four regions, indicating lower activity of pyramidal neurons. The similar alterations of BDNF and NPTX2 mRNAs across the four regions could reflect reduced activity of pyramidal neurons selectively expressing these transcripts as well as dysregulation of GABA neuron phenotypes, both of which could contribute to the regionally conserved alterations of PV and SST neurons in the vsWM network in SZ. Lower levels of ADCYAP1 and NRN1 mRNAs limited to occipital regions might suggest regional differences in the effect of SZ on the activity of pyramidal neurons selectively expressing these transcripts and/or the transcriptional regulation of these transcripts by neuronal activity.

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CRediT authorship contribution statement

Yufan Bian: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Rika Kawabata:** Writing – review & editing, Investigation, Formal analysis. **John F. Enwright:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Makoto Tsubomoto:** Writing – review & editing, Investigation, Formal analysis. **Takeshi Okuda:** Writing – review & editing, Investigation, Formal analysis. **Kohei Kamikawa:** Writing – review & editing, Investigation. **Sohei Kimoto:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Mitsuru Kikuchi:** Writing – review & editing, Project administration, Formal analysis. **David A. Lewis:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Takanori Hashimoto:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary materials

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