Title: A Kainate receptor GluK4 deletion, protective against bipolar disorder, is associated with enhanced cognitive performance across diagnoses in the TwinsUK cohort

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Abstract

Objectives: Cognitive deficits are a common feature of neuropsychiatric disorders. We investigated the relationship between cognitive performance and a deletion allele within GluK4 protective against risk for bipolar disorder, in 1642 individuals from the TwinsUK study.

Methods: Cognitive performance was assessed using the National Adult Reading Test, four CANTAB tests (Spatial Working Memory, Paired Associates Learning, Pattern Recognition Memory, and Reaction Time), and two Principal Component Analysis derived factors. Performance in individuals homozygous for the insertion allele was compared to deletion carriers and analysis was adjusted for age of diagnosis, medication and clinical diagnosis.

Results: Individuals with the GluK4 protective deletion allele performed significantly better in Spatial Working Memory compared to insertion homozygotes when adjusted for a clinical diagnosis. GluK4 deletion carriers who had a mental health problem (predominately depression) showed better performance in visuo-spatial ability and mental processing speed compared to individuals with mental health problems homozygous for the insertion.

Conclusions: These findings of genotype-dependent cognitive enhancement across clinical groups support the potential clinical use of the GluK4 deletion allele in personalized medicine strategies and provide new insight into the relationship between genetic variation and mood disorders.

Key words: Kainate receptors, GluK4, deletion allele, cognition, mood disorders

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Disclosure of interest

The authors report no conflicts of interest

Introduction

Mood disorders including bipolar disorder, major depression and anxiety disorders are highly heritable, indicating that genetic or heritable epigenetic components contribute to risk of developing disease (Cross-Disorder Group of the Psychiatric Genomics *et al.*, 2013; Genetics of Personality *et al.*, 2015; McCarthy *et al.*, 2014; Song *et al.*, 2015). Large genome-wide association studies and whole genome sequencing studies have identified common and rare variants which implicate shared neurobiological pathways including glutamate neurotransmission involving NMDA, AMPA and KAR receptors (Singh *et al.*, 2017; Teng *et al.*, 2017; Witt *et al.*, 2017). *De novo* and inherited structural variants and point mutations have been identified as risk variants within glutamate subunit receptor genes (Frank *et al.*, 2011; Hamdan *et al.*, 2011; Kirov *et al.*, 2012). These genetic findings support the view that disruption of the glutamatergic system contributes to the pathophysiology of mental illnesses.

Kainate receptors are ionotropic glutamate receptors involved in cellular functions necessary for learning and memory, such as synaptic plasticity, long-term potentiation and neurotransmission (Bortolotto *et al.*, 1999; Bortolotto *et al.*, 2005; Lerma *et al.*, 2013; Schmitz *et al.*, 2003; Sihra *et al.*, 2014; Sihra *et al.*, 2013). They are composed of tetrameric combinations of five subunits (GluK1-GluK5; encoded by *GRIK1-GRIK5*) and modulated by auxiliary proteins Neto1 and Neto2 (Han *et al.*, 2016; Jane *et al.*, 2009; Kristensen *et al.*, 2016; Lerma *et al.*, 2001; Li *et al.*, 2016; Traynelis *et al.*, 2010). We have previously reported *GRIK4*/GluK4 as a breakpoint gene disrupted in a complex chromosomal rearrangement in a patient diagnosed with schizophrenia co-morbid with learning disability (Pickard *et al.*, 2008; Pickard *et al.*, 2006). Subsequent case control genetic studies led to the identification of a 14 base pair deletion variant

(indel) (rs869187535) within the 3' untranslated region of the gene which was negatively associated with bipolar disorder (Knight *et al.*, 2012; Pickard *et al.*, 2006).

A significant increase in RNA and protein GluK4 expression in the frontal cortex and hippocampus correlating with the deletion allele provided some indication that subunit availability in specific neuronal populations such as the CA3 mossy fibre region might underlie this protective effect (Knight *et al.*, 2012; Pickard *et al.*, 2008). Consistent with this model, individuals with the deletion allele were reported to show greater left hippocampal activation than insertion homozygotes during a cognitive face processing task (Whalley *et al.*, 2009).

Rodent behavioural studies have provided additional evidence that GluK4 receptor subunit function contributes to neuropsychiatric phenotypes and memory function. For example, GluK4 knockout mice demonstrate hippocampal-dependent cognitive impairments, marked hyperactivity and impaired pre-pulse inhibition which reflect aspects of a schizophrenic phenotype (Lowry *et al.*, 2013), whereas mice overexpressing Grik4 in the forebrain show anhedonia, depression, anxiety, altered social interaction and synaptic transmission, features consistent with an autism spectrum disorder phenotype (Aller *et al.*, 2015).

Large scale genome-wide pharmacogenetics studies have also reported an association between variants within GluK4 and response to antidepressant treatment. For instance, variants in the 3' region of GluK4 identified in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial were found to affect patients' response to citalopram antidepressant treatment (Paddock *et al.*, 2007). Subsequently, intronic variants within GluK4 have now been consistently reported as moderating both antidepressant and antipsychotic efficacy and tolerability (Drago *et al.*, 2013).

The aim of this study was to compare cognitive performance in subjects carrying the protective 3'UTR GluK4 deletion with subjects homozygous for the insertion genotype, in members of the TwinsUK population cohort in order to assess whether the GluK4 deletion genotype could be a marker of protection against developing disease-associated cognitive deficits. Clinical data is available which allows the TwinsUK Cohort to be divided into subsets of individuals with various psychiatric and neurological disorders. Information is also available on current and past use of antidepressant, antipsychotic and antiepileptic medication. We hypothesized that carriers of the deletion allele would perform better than individuals homozygous for the insertion in tasks assessing specific aspects of cognition. We analysed cognitive test data, controlling for medication use, in members of the TwinsUK cohort with known GluK4 indel genotype status.

Materials and methods

Sample population

The TwinsUK cohort is a repository of approximately 12,000 monozygotic and dizygotic British twins who have been serially assessed for health traits. Procedures used for sample and data collection have been described previously (Spector *et al.*, 2006). TwinsUK was approved by the Guy's and St Thomas' Ethics Committee. Phenotypic data for TwinsUK was requested and approved through the TwinsUK Resource Executive Committee (TREC) based at the Department of Twins Research and Genetic Epidemiology at Kings College London. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Baseline phenotypic measurements were

taken between 1992 and 2004 followed by multiple surveying sweeps and clinical visits. Recruitment to the TwinsUK cohort was voluntary. Individuals included in this analysis are all female. The ages ranged from 17 to79 years with a mean of 49 years.

Genotype Data

The aim of the UK10K project is to genome-wide sequence and deeply phenotype cohorts to assess the role of genetic variants in health and disease (Walter *et al.*, 2015). Genotype data for the TwinsUK cohort was accessed from the European Genome-phenome Archive (EGA; accession numbers EGAD00001000194 & EGAD00001000741) following a data access agreement with the UK10K project. Permission to link the genotype and phenotype data was also granted by TREC.

Processing of next generation whole exome sequencing was performed by the Wellcome Trust Sanger Institute (Cambridge) using GATK and mapped to build GRCh37/hg19. Sequencing Variant Calling Files (VCFs) were downloaded from the EGA website and the VCFtools program was used to splice out the GluK4 co-ordinates [chr11:120,511,746 bp – 120,988,904 bp] from each VCF file. Selected BAM files were downloaded and processed using SAMtools and visualised using IGV to confirm sequencing quality in the region of the indel. The minor allele frequency of the deletion in the general population (MAF) is ~0.21 and individuals identified as carrying either one (heterozygous) or two (homozygous) copies of the deletion were grouped as deletion carriers. We obtained access to genetic data for 1870 individuals. Of these, there were no processed sequencing data for 184 individuals and forty-four individuals were excluded because of low sequencing read depth and poor sequencing quality. A total of 1642 individuals remained of which 1158 were homozygotes for the insertion genotype (HOM INS) and 484 deletion allele carriers (DEL).

Cognitive Tests

Cognitive performance was assessed by the National Adult Reading Test (NART), which is widely accepted as an estimate of premorbid intelligence levels, and four Cambridge Neuropsychological Test Automated Battery (CANTAB) tests; the spatial working memory task (SWM), paired associates learning (PAL), reaction time (RTI), and the pattern recognition memory task (PRM). SWM assesses the retention and manipulation of visuospatial information, and the outcome measure used was the number of errors. PAL assesses visual memory and new learning, and the outcome measure used was the number of errors. RTI provides an assessment of motor and mental response speeds. PRM is a test of visual pattern recognition memory in a two-choice forced discrimination paradigm, with the outcome measure being the speed of subjects' responses. Principal Component Analysis using each cognitive test outcome measure was performed to identify domains of cognition which may have differed between individual groups.

Diagnostic groups and medication status

Information about clinical diagnosis and medication history was provided by TREC, Department of Twins Research and Genetic Epidemiology at King's College London. The initial TwinsUK survey grouped participants into three diagnostic groupings; "learning disabilities", "mental health problems" and "other neurological disorders". For the current analysis we retained the three main diagnostic groupings but excluded cases with learning disability or epilepsy from the "mental health problems" group because both learning disability and epilepsy are associated with specific patterns of cognitive deficits. The "learning disabilities" group included individuals both with and without co-morbid "mental health problems". Secondly all individuals with a diagnosis

of epilepsy, some of whom were co-morbid with learning disabilities or mental health problems, were included in a single "epilepsy" group.

This gave a total of five diagnostic groups: no clinical phenotype (N=1071), learning disability (N=23); mental health problems (N=259); epilepsy (N=231); other neurological diseases (N=58). The "mental health problem" group included individuals with a diagnosis of clinical depression (163), bipolar disorder (2), anxiety and stress-related disorders (31), eating disorders (15) and 48 individuals with mental health problems about which no clear definition was available. The "other neurological disorders" group included neuropathies, stroke, multiple sclerosis, migraine and Parkinson's disease. Analysis using these specific diagnostic groups was conducted only when the number of individuals exceeded 10 in each group.

Current and past medication status was obtained: individuals who receive no regular medication (N =365), antidepressants (N =150), antipsychotics (N =45). Individuals without diagnostic information who had taken antipsychotic, antidepressant or anti-epileptic medication in the past, were included within the mental health alone and epilepsy subgroupings.

Statistical analysis

Pearson's correlation coefficient (r) was calculated to examine correlations between individual cognitive tests. Cognitive data was tested for a normal distribution using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. If data did not show a normal distribution, the logarithm of the values was used for further analysis. No outliers were identified or removed. PCA using each cognitive test outcome measure was performed to identify latent factors representing domains of cognition which may have differed between individual groups. The output variables from PCA were measured with the

Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and the Barlett's test of sphericity.

Multivariate linear regression analyses were used to compare cognitive performance between the genotype groups. The derived diagnosis and medication variables were included as covariates. Z-scores of cognitive performance were generated and used to compare genotype, diagnosis and medication group relationships. Pearson's chi-squared tests were performed to examine differences between diagnosis and medication status. As we hypothesized that carriers of the GluK4 deletion allele will perform better in the cognitive tests, statistical analysis was one-tailed and statistical significance was considered at $p < 0.05$.

Results

Comparison of cognitive test outcome measures

Table 1 presents the Pearson's correlation coefficients between each cognitive test outcome measure. Errors in paired associates learning (PAL) showed a significant positive correlation with spatial working memory task (SWM) errors ($r > 0.39$, $p < 0.001$), and with latency in the pattern recognition memory (PRM) ($r > 0.26$, $p < 0.001$) and reaction time (RTI) ($r > 0.26$, $p < 0.001$) tests. SWM errors also showed a significant positive association with RTI latency ($r > 0.18$, $p < 0.01$). As would be expected for two tests which assess mental response speed, PRM and RTI latency were also correlated ($r > 0.24$, $p < 0.0001$). There was no significant correlation between performance on the NART test and any of the CANTAB performance, supporting the

distinction between general intelligence measured by NART and specific facets of cognition evaluated by the CANTAB tasks.

Insert Table 1 here.

Principal Component Analysis (PCA) identified two derived cognitive factors. The first factor included PAL errors (component loading 0.59), PRM latency (component loading 0.74), RTI latency (component loading 0.74), RTI latency (component loading 0.67), and NART score (component loading 0.32) as presented in Table 2. As performance in these measures is associated with visuospatial mnemonic indices and speed of response, we refer to this factor as 'visuo-spatial ability and mental speed'. The second factor comprised of performance in PAL errors (component loading 0.53), and SWM errors (component loading 0.73), and NART score (component loading -0.675), shown in Table 2. As this grouping includes general intelligence, response times and errors in visual discriminatory we refer to this factor as 'general intelligence and visual discrimination'.

Insert Table 2 here.

Cognitive performance and GluK4 genotype

Table 3 presents the mean, standard error (SEM), *F* statistic, *p* values and partial-eta^2 (hp^2) effect size for cognitive performance for the two genotype groups (HOM INS homozygous insertion versus DEL deletion carriers), unadjusted and adjusted and for co-variance with diagnosis. Cognitive performance profiles for each genotype are also presented as Z-scores in Figure 1. As indicated in Figure 1A, DEL carriers displayed more variance in cognitive performance compared to HOM INS individuals. Only one task, the SWM CANTAB task, showed a trend towards significance when comparing

performance scores in the two genotype groups (HOM INS 1.57 ± 0.019; DEL 1.51 ± 0.035) (Figure 1B). This trend became significant when diagnosis was included as a co-variate ($F = 3.056$, $p = 0.041$, $hp^2 = 0.017$) with the DEL carriers making fewer SWM errors than the HOM INS individuals. No difference between the two genotype groups was observed for performance in either of the derived PCA factors.

Insert Figure 1 here. Insert Table 3 here.

Cognitive performance and diagnosis of neurological and mental disorders

Of the 1642 TwinsUK cohort members assessed, 571 individuals were reported to have a diagnosis of a mental health or neurological disorder. As these diagnoses were varied and often co-morbid, individuals with a diagnosis were categorized into the following groups: mental health problems alone (MH) N = 259; learning disability including learning disability with mental health problems (LD/LD & MH) N = 23; epilepsy including epilepsy co-morbid with other conditions (EP) N = 231; and, other neurological diseases (Other) N = 58. The numbers per diagnostic group for the GluK4 indel genotype groups are presented in Table 4. No difference in diagnosis was observed with genotype status ($\chi^2 = 0.602$, df = 4, $p = 0.963$).

Within these respective diagnostic groupings, cognitive performance in two measures was found to differ between the genotypes. DEL carriers performed better than HOM INS individuals within the 'mental health problems alone' group (MH) in the derived 'visuospatial memory and mental speed' derived factor (N = 259, F = 3.176, df = 1, $p = 0.043$, $hp^2 = 0.102$). In addition, a significant statistical difference in NART scores within the 'other neurological disorders group' was evident (N = 58 F = 8.006, df = 1, $p = 0.009$, $hp^2 = 0.235$), where again GluK4 DEL carriers showed better performance in this general IQ test than HOM INS individuals (Figure 1C). Although the numbers

within each group were relatively small, the effect sizes for these genotype differences in performance were relatively large.

Insert Table 4 here.

Cognitive performance and medication

Cohort members who reported a history of taking antipsychotic, antidepressant or antiepileptic medication were assessed in conjunction with diagnostic history (Figure 1B). Table 5 presents the number of individuals on each type of medication in total and split by genotype group. 195 individuals were reported to have taken medication and had a diagnosis of disease, corresponding to ~12% of the total number of individuals with diagnosis and medication status both available (Figure 1B). However, 74 individuals had no reported history of medication (they did not receive daily medication for over one month) but had a diagnosis. This corresponded to a ~4.5% of the total number of individuals with a diagnosis and medication status both available (Figure 1B).

To investigate the relationship between medication and the GluK4 indel genotype, individuals were categorized as taking antidepressants, other medication (antipsychotics, benzodiazepines, barbiturates) or no medication. Table 5 presents the number of individuals on each type of medication in total and for the separate genotype groups. The number of individuals who had taken antidepressant medication or other medication showed no difference between the genotype groups ($\chi^2 = 0.653$, df = 2, $p = 0.722$). Differences in cognitive performance were assessed between GluK4 HOM INS individuals and DEL carriers who took no medication and individuals who received either antidepressants, antipsychotics or other medication. The effect of taking

medication was found not to influence cognitive performance between the two genotype groups ($p > 0.259$ for all cognitive tests).

Insert Table 5 here.

Discussion

Impairments in working memory, attention and executive function are amongst the main cognitive deficits found in schizophrenia, bipolar disorder depression, and anxiety (Ferreri *et al.*, 2011; Millan *et al.*, 2012). We tested the hypothesis that a deletion variant within GluK4 reported to confer protection against developing bipolar disorder would show an association with better cognitive performance in a number of domain-specific cognitive tasks in unaffected individuals, and in individuals with "mental health problems", learning disabilities and individuals with "other brain diseases".

The cognitive profile of 1642 individuals from the TwinsUK study indicated a significant difference in spatial working memory performance between the DEL carriers and HOM INS genotype groups in the "mental health problems " group who almost entirely came under the umbrella diagnosis of "mood disorders", mainly depression and anxiety. Consistent with previous research, we discovered that DEL carriers made fewer errors in spatial working memory. We also found that DEL carriers who had a mental health illness showed better performance in 'visuo-spatial ability and mental speed' than HOM INS individuals.

Furthermore, DEL carriers within the 'the other neurological disorders' group showed better performance in the National Adult Reading Test, NART, than HOM INS individuals. As NART is a test which is commonly used to assess premorbid

intelligence, i.e. more general cognitive ability, we might expect more general deficits which are not domain specific to be evident in a group who has neurological diseases which include Parkinson's disease, stroke, neuropathy, multiple sclerosis and migraine (McGurn *et al.*, 2004). However, our findings show that although there was overall no difference in NART between this diagnostic grouping and the others assessed, there was a highly significant genotype effect for NART scores, with DEL carriers performing better than HOM INS individuals. This would suggest that the GluK4 indel allele could be relevant to a broader disease phenotype than has previously been investigated and therefore has the potential to be a biological marker of function relevant to neurological disease prognosis. Future studies should aim to explore further the neuroprotective role of GluK4 deletion allele through both preclinical and neurological disease cohort studies.

The current study also provides evidence that an allele which modulates GluK4 protein abundance in both the frontal cortex and hippocampal regions such as the CA3 and dentate gyrus granule cells, is also involved in modulating memory function associated with hippocampal neuronal circuitry. We found that healthy and disease affected deletion carriers performed better in SWM, a test which involves hippocampal processing, i.e. the contextual component of spatial memory. These findings are consistent with the report that non-diseased GluK4 deletion carriers show increased hippocampal activity during a face-processing task (Whalley *et al.*, 2009).

However, in contrast to our predictions, a difference in performance on the hippocampal-dependent CANTAB PAL test was not clearly shown. Nevertheless, DEL carriers who were identified as having a mental health problem performed better in the PCA-derived cognitive factor which included fewer errors in PAL, faster reaction time in visual pattern recognition (PRM) and visual object processing (RTI), indices which

are all dependent on the 'what', 'where' and 'when' components of contextual hippocampal processing. We speculate that the underlying mechanism may involve decrease in GluK4 receptor function associated with the insertion allele, adding to an already maladaptive, allostatic dysregulation of key neurotransmitter systems in individuals with mental health disorders, which results in disrupted processing within specific pathways and regions of the brain and impairment in distinct affiliated cognitive domains. Further neuropsychological testing combined with brain imaging of healthy and diseased cohorts may help to elucidate which additional brain structures are of importance to this GluK4 indel genotype effect.

The use of pharmacogenetics to predict patients' response to antidepressant treatments has become an increasingly important goal. Previous studies have identified variants within GluK4 which showed significant association with antidepressant and antipsychotic treatment efficacy. Although no difference between the genotypes was observed in the number of individuals on medication and different medication types, the number of individuals taking medication was low and we could not investigate treatment response. Therefore, it is possible that the GluK4 indel could also contribute to a similar pharmacogenetics effect. Further studies will be needed to examine whether the GluK4 indel could be a valid human biomarker helpful in identifying drugs with a significant risk of reducing depression during clinical use.

Findings from recent GWAS array and next generation sequencing exome studies of affected populations and multigenerational pedigrees, indicate shared genetic variation contributing to risk for schizophrenia, bipolar disorder as well as other brain diseases (Cross-Disorder Group of the Psychiatric Genomics, 2013; Knight *et al.*, 2009; Singh *et al.*, 2017). One such large GWAS study recently reported an association between

high frequency variants of small effect spanning the major histocompatibility complex (MHC) and risk for schizophrenia and bipolar disorder (International Schizophrenia *et al.*, 2009). Subsequent studies examining this locus identified multiple risk haplotypes composed of common alleles within the complement component 4 (*C4*) gene (Sekar *et al.*, 2016). Although the C4 gene is involved in the immune system classical complement cascade, the C4 protein is highly expressed in post synaptic compartments in neurons. Of interest, members of a second complement cascade protein family (C1ql2 and C1ql3) are also located at postsynaptic sites and are known to bind directly to the amino-terminal domains of kainite GluK2 and GluK4 KAR receptor subunits and hence regulate recruitment and function of ionotropic glutamate receptors at synapses (Matsuda, 2017).

Unlike many other genes found associated with mental illness, GluK4 research has provided consistent and replicated findings linking risk for mood disorders with molecular and proteomic changes, neurotransmission deficits and differential brain regional activity. The current novel findings suggest that the deletion allele also contributes to improved non domain-specific general cognitive ability in individuals with neurological diseases as well as better performance in domain-specific hippocampal dependent cognition in individuals with mood disorders. These studies show the potential clinical utility of the GluK4 indel in personalized medicine strategies and provide new insight into the relationship between genetic variation, neurobiology and disease.

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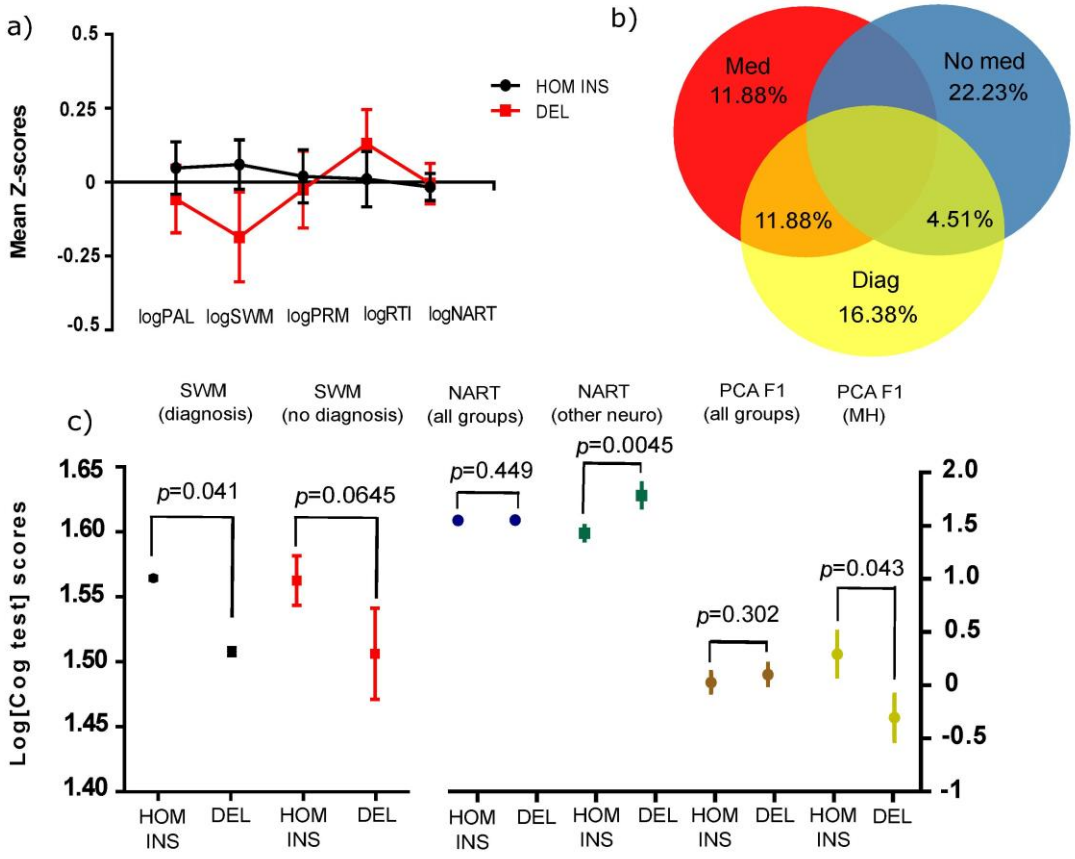

Figure 1. **Cognitive performance as grouped by genotype status and specific diagnostic groups and relationship between self-reported medication and diagnosis**. **Panel A** The cognitive profile of *GRIK4* DEL carriers and HOM INS homozygotes when diagnosis is added as a co-variate factor. The mean of Z-scores of each cognitive test and SEM is displayed for each genotype group. **Panel B** Venn diagram showing the percentage of overlap between medication group (red – "Med"), no medication group (blue – "No med") and diagnosis (yellow – "Diag"). **Panel C** Cognitive performance for both genotypes in the SWM task with and without diagnosis as a co-variate, and, performance in NART and PCA Factor 1 (visuospatial memory and mental speed) within the other neurological disorders group and mental health problems group respectively. Cognitive performance is shown as logged test scores and *p*-values less than 0.05 indicate a significant difference in performance. Other neuro

denotes ‘other neurological disorders’ group and MH denotes ‘mental health problems’ group.

logPAL: logged paired associates learning, logSWM: logged spatial working memory, logPRM: logged pattern recognition memory, logRTI: logged reaction time, logNART: logged national adult reading test, SWM: spatial working memory, NART: national adult reading test, PCA F1: PCA Factor 1, Med: medication, No med: no medication, Diag: diagnosis.

	logPAL	logSWM	logPRM	logRTI	logNART
logPAL	-	0.399***	0.264***	0.262***	-0.077
logSWM		-	0.030	0.185**	-0.120
logPRM			-	0.243***	0.075
logRTI				-	0.011
logNART					-

Table 1: Correlation coefficients between cognitive performance in individual tests and derived cognitive factors. Positive Pearson's r values indicate a positive correlation between test performances whilst negative values indicate a negative correlation. NART performance does not show a correlation with the attention and memory tests, whereas there is a positive association between the SWM, PAL and RTI tests. r values are significant at either the $p < 0.05$ (*) , $p < 0.01$ (**) or $p < 0.001$ (***) level. SWM: spatial working memory, NART: national adult reading test, PRM: pattern recognition memory, RTI: reaction time, PAL: paired associates learning.

	Component	
	PCA F1 Visuo-spatial ability and mental speed	PCA F2 General intelligence and visual discrimination
PAL errors	0.593	0.525
SWM errors		0.731
PRM latency	0.742	
RTI latency	0.670	
NART score	0.316	-0.675

Table 2: PCA component loadings for the two derived factors; visuo-spatial ability and mental speed, and general intelligence and visual discrimination. "PCA F1" denotes a 'visuo-spatial ability and mental speed' factor and "PCA F2" denotes a 'general intelligence and visual discrimination' factor. SWM: spatial working memory, NART: national adult reading test, PRM: pattern recognition memory, RTI: reaction time, PAL: paired associates learning.

Cognitive test	HOM INS Mean (SEM)	DEL Mean (SEM)	hp^2	*P*-Value	hp^2 With diagnosis	*P*-value With diagnosis
logSWM	1.56 (0.019)	1.51 (0.035)	0.013	0.065	0.017	0.041*
logNART	1.55 (0.016)	1.55 (0.023)	0.000	0.445	0.000	0.449
logPRM	3.33 (0.010)	3.33 (0.014)	0.000	0.390	0.000	0.388
logRTI	2.57 (0.006)	2.58 (0.008)	0.003	0.228	0.001	0.369
logPAL	1.43 (0.018)	1.41 (0.023)	0.003	0.247	0.006	0.138
Visuo-spatial ability & processing speed	0.02 (0.097)	0.01 (0.102)	0.000	0.462	0.002	0.302
General intelligence and memory speed	0.09 (0.095)	-0.16 (0.121)	0.012	0.068	0.014	0.055

Table 3: Mean cognitive performance in TwinsUK cohort members as grouped by genotype status. Mean, standard error (SEM), effect size (partial-eta squared, (hp^2) and *p* values are presented. Statistical values are also presented when diagnosis is added as a covariate. HOM INS: homozygotes for the insertion genotype, DEL: deletion allele carriers, SWM: spatial working memory, NART: national adult reading test, PRM: pattern recognition memory, RTI: reaction time, PAL: paired associates learning.

Diagnosis	Data*	INS/INS	DEL
No diagnosis	1071	751 (70.1%)	320 (29.9%)
Mental health problems	259	183 (70.7%)	76 (29.3%)
LD and LD with mental health	23	17 (73.9%)	6 (26.1%)
Epilepsy and comorbid epilepsy	231	164 (71.0%)	67 (29.0%)
Other neurological disorders	58	43 (74.1%)	15 (25.9%)

Table 4: Clinical diagnosis status of individuals in the genotype groups, HOM INS and DEL carriers. Numerical values indicate the actual numbers of individuals for each diagnosis group and in each genotype group. Percentages indicate the number of individuals per genotype group for each diagnostic group. The asterisk (*) symbolizes the number of genotyped individuals within each diagnosis group. HOM INS: homozygotes for the insertion genotype, DEL: deletion allele carriers.

Medication	All	INS/INS	DEL
No “daily” medication	365	257 (70.4%)	108 (29.6%)
Antidepressants	150	104 (69.3%)	46 (30.7%)
Others (Antipsychotics, BDZ, Brb)	45	34 (75.6%)	11 (24.4%)

Table 5: Medication status of individuals in the HOM INS and DEL carrier genotype groups. The percentages and numbers of each medication and no “daily” medication group are shown in the “All” column. Numerical values indicate the actual numbers of individuals for each medication group and per genotype group. “BDZ” and “Brb” denote treatment with benzodiazepines or barbiturates respectively. HOM INS: homozygotes for the insertion genotype, DEL: deletion allele carriers.