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Title:
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Date:
2022-11-01

Citation:
Dean, B., Thomas, E. H. X., Bozaoglu, K., Tan, E. J., Van Rheenen, T. E., Neill, E., Sumner, P. J., Carruthers, S. P., Scarr, E., Rossell, S. L. & Gurvich, C. (2022). Evidence that a working memory cognitive phenotype within schizophrenia has a unique underlying biology.. Psychiatry Research, 317, https://doi.org/10.1016/j.psychres.2022.114873.

Persistent Link:
https://hdl.handle.net/11343/332739

Evidence that a working memory cognitive phenotype within schizophrenia has a unique underlying biology.

Running Title: **Peripheral Gene Expression in Schizophrenia**

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Abstract

It is suggested studying phenotypes within the syndrome of schizophrenia will accelerate understanding the complex molecular pathology of the disorder. Supporting this hypothesis, we have identified a sub-group within schizophrenia with impaired working memory (WM) and have used Affymetrix™ Human Exon 1.0 ST Arrays to compare their blood RNA levels (n=16) to a group of with intact WM) (n=18). Levels of 72 RNAs were higher in blood from patients with impaired WM, 11 of which have proven links to the maintenance of different aspects of working memory (cognition). Overall, changed gene expression in those with impaired WM could be linked to cognition through glutamatergic activity, olfaction, immunity, inflammation as well as energy and metabolism. Our data gives preliminary support to the hypotheses that there is a working memory deficit phenotype within the syndrome of schizophrenia with has a biological underpinning. In addition, our data raises the possibility that a larger study could show that the specific changes in gene expression we have identified could prove to be the biomarkers needed to develop a blood test to identify those with impaired WM; a significant step toward allowing the use of personalised medicine directed toward improving their impaired working memory.

Keywords: gene expression, cognition, glutamate, olfaction, immunity, inflammation, energy and metabolism, biotypes, biomarkers, biological markers

Introduction

Schizophrenia is diagnosed following the appearance of a constellation of symptoms that can be clustered into positive, negative and cognitive domains (Kirkpatrick et al., 2001). This approach to diagnosing schizophrenia means it is a clinical syndrome encapsulating a number of disorders (Smigielski et al., 2020). The concordance rate of < 50% for developing schizophrenia between monozygotic twins (Onstad et al., 1991) gives a strong indication that disorder is not simply due to heritability. Rather, schizophrenia occurs in those with an inherited genetic susceptibility after they have encountered deleterious environmental factor/s (Smigielski et al., 2020). The environmental impact triggering schizophrenia would affect epigenetic mechanisms which, along with genetic mutations, would cause changes in gene expression (Richetto and Meyer, 2020). Thus, it is reasonable to conclude that changed gene expression contributes to the aetiologies of schizophrenia; a hypothesis supported by studies showing extensive changes in gene expression linked to a number of biochemical processes in the CNS from patients with the disorder (Bray, 2008; Fillman et al., 2013; Hoffman et al., 2019; Horvath and Mirnics, 2015; Jaffe et al., 2018; Mirnics et al., 2000; Narayan et al., 2008; Scarr et al., 2018a; Scarr et al., 2018b; Wu et al., 2021).

The intensive study of the genetics of schizophrenia has shown it to be a highly polygenic and complex disorder (Smeland et al., 2020). This has led to the suggestion that understanding the pathophysiology of schizophrenia will require the study of more homogenous sub-groups within that complex syndrome (Tamminga et al., 2017). The study of gene expression in postmortem CNS has allowed some progress toward this goal by defining sub-groups within schizophrenia based on changes in a single molecule (Scarr et al., 2009) or a defined biochemical pathway (Fillman et al., 2013). However, growing data is suggesting sub-groups

may be identified based on presentation of different symptom constellations (Dwyer et al., 2020). This approach highlights a significant limitation of studying gene expression in post-mortem CNS, which is the difficulty in identifying sub-groups based on clinical data because of the limitations of retrospective case-history reviews in collecting useful information on both the diversity of symptoms and their severity during what are often long durations of illness (Hill et al., 1996). Thus, to attempt to establish a link between clinical based sub-groups and their potential underlying biology, studies are using gene expression and other technologies to get measurements at the "omics" level from blood cells to identify potential links between symptom based sub-groups and their underlying biology (Fillman et al., 2016; Glen et al., 1994; Lai et al., 2016; Urhan-Kucuk et al., 2011).

When considering behaviour-based phenotypes, it is notable that cognitive deficits are a core feature of schizophrenia and that cognitive ability has a genetic component but is also influenced by environmental factors (Antonucci et al., 2020). Substantial cognitive deficits are reported in approximately 80% of people with schizophrenia (Carruthers et al., 2019; Van Rheenen et al., 2017) and it has been shown that cognitive deficits in people with schizophrenia have varying severity across numerous cognitive domains (Mesholam-Gately et al., 2009), respond poorly to antipsychotic drug treatment (Park et al., 1999) and can be detected before the onset of psychosis (Caspi et al., 2003). Together these findings argue that cognitive phenotypes within schizophrenia may be detectable early in the onset of the disorder and would be present in both drug-naïve and treated individuals.

It has been argued that cognitive ability, independent of psychiatric illness, may be associated with the functionality of specific biochemical pathways in the CNS (Dean et al., 2020; Dean and Scarr, 2016; Parkin et al., 2018; Scarr et al., 2012) and that such changes are in part

modulated by differential changes in gene expression in the CNS of people with varying cognitive ability (Dean et al., 2020). Several studies have demonstrated the potential of using data driven cognitive clustering to derive more homogenous phenotypic subgroups to examine the neurobiological underpinnings of cognitive deficits (Fernandez-Linsenbarth et al., 2021; Gurvich et al., 2022; Wenzel et al., 2021). This research provides some validation to searching for levels of gene expression in blood that may be differentially associated with clusters of impaired versus intact cognitive performance in subgroups within disorders that include people with clear cognitive impairments, such as schizophrenia. It is therefore significant that one study has reported that blood levels of RNA for genes, which act to suppress WNT signalling could be used to predict cognitive impairment in patients with the disorder (Wu et al., 2016). Another study reported levels of RNA for genes involved in immune or inflammatory mechanisms being linked to deficits in verbal working memory in schizophrenia (Ukkola-Vuoti et al., 2019). In addition, a study of gene expression in blood from patients with schizophrenia, their unaffected co-twins and controls found changes in gene expression in individuals that were associated with verbal memory impairments independent of diagnoses (Zheutlin et al., 2016). These findings highlight the potential usefulness of focusing on gene expression changes in working memory specifically.

Among the cognitive deficits associated with schizophrenia, it is notable that dysfunction of verbal working memory, a cognitive process that mediates short-term information storage and manipulation, is reported to be a core and robust symptom of the disorder (Forbes et al., 2009). Hence, in this study we determined if it was possible to cluster individuals with schizophrenia and impaired working memory (WM) and whether such a cluster had changes in blood gene expression compared to a cluster with schizophrenia and intact WM.

Methods

Ethical Approval

Ethical approval for this research was from the Alfred Hospital Human Research Ethics Committee operating in accordance with the Declaration of Helsinki. Written informed consent to participate in this study was obtained from each participant.

Participant Recruitment

Recruitment was by a variety of techniques that included online advertising, community notice boards, as well as face to face recruitment through inpatient and outpatient services. Possible participants were initially screened by telephone interview to determine if they met the inclusion criteria of being between 18 and 64 years of age, being able to provide informed consent, having a first language of English or having primarily spoken English for over 10 years. Exclusion criteria were significant head injuries, a loss of consciousness > 5 minutes (including from drug overdose), a diagnosis or being medicated for of an anxiety or a depressive disorder and, within 6 months of screening, having a history of substance abuse or having received electroconvulsive shock therapy.

Diagnosis and Blood Collection

For each recruit, a DSM-IV diagnosis of schizophrenia was confirmed using the MINI International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997), psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

All participants in the study completed a demographic interview and a neuropsychological testing battery that included assessments of premorbid intelligence (Wechsler Test of Adult Reading (WTAR)) and cognition (Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery) (Nuechterlein et al., 2008).

Blood samples for this study were collected from each patient into a Tempus^{TM} Blood RNA tube (Thermo Fisher Scientific, Scoresby, Victoria, Australia) on the day of testing.

Cluster Analysis

The data from the Letter Number Span and Digit Span backwards from each recruit was analysed with a two-step cluster analysis using Akaike's Information Criterion with Euclidean distance. Hierarchical agglomerative clustering, with Ward's minimum variance method and Squared Euclidean distance, was used to confirm the number of cluster subgroups within schizophrenia.

Statistics: Group Demographics

Student t-tests were used to identify group differences in the demographic data between patients with impaired WM and intact WM. X^2 tests were used to identify any variation in frequency of non-continuous data sets between the two groups of cohorts.

RNA extraction, Microarray Processing and Data Analyses

RNA was prepared from the 5 ml of whole blood in a Tempus^{TM} Blood RNA tube according to the blood tube manufacturer's instructions. The purity of RNA was assessed using the 260 / 280 ratio measured using a NanoDrop UV-Vis Spectrophotometer. A 260 / 280 ratio of close to 2.0 was required for a donor RNA to be included in this study.

RNA was sent to the Ramaciotti Centre for Genomics at the University of New South Wales where ribosomal mRNA was eliminated and random priming used to generate cRNA that was end labelled with biotin using the Affymetrix synthesis and labelling kit. Samples, when they had passed a further quality check, were prepared for hybridisation using a standard probe cocktail. Each sample was loaded into an Affymetrix™ Human Exon 1.0 ST Array (Affymetrix, Santa Clara, CA, USA) and hybridised overnight. Following post-hybridization washes, the chips were scanned and the fluorescent signals converted into a DAT file. After visual confirmation of the scans and quality control analysis, these files were used to generate subsequent cell intensity (CEL) and chip files for analysis.

Analyses using the cell intensity (CEL) and chip files were as described previously (Scarr et al., 2018a, 2019; Scarr et al., 2018b). Hence, data from all the CEL files were imported into JMP Genomics 9.0 (SAS, Cary, NC, USA) at the gene level, collapsing the exon-level data onto known transcripts. To control for array-to-array variation, the data were normalised using the Robust Multichip Average (RMA) algorithm. The data were then log2 transformed and, because they were to be analysed across multiple groups, normalised for between-group comparisons using the 'Least Square means' method (Scarr et al., 2018b) and then imported using metaprobe set and probe set list files. Once the analytical data was imported RNA levels in impaired WM and intact WM were compared. These analyses followed a well-defined strategy for analysing expression microarrays data (Maqc Consortium et al., 2006), which uses

the criteria of a non-stringent group-wise P-value cutoff of 0.01 with a fold change of ≥ ± 20% to define meaningful changes in levels of RNA. We have previously used real-time quantitative PCR to show this approach limits false positive results to ≤ 10% (Narayan et al., 2008; Scarr et al., 2018b). Reflecting the size of our study cohorts, we did not use a false discovery rate as this would have overwhelmingly called true positive results as false positives (Benjamini and Hochberg, 1995; Tong and Zhao, 2008).

Gene expression: Ingenuity Pathway Analysis

IPA Core Analysis (IPA: https://digitalinsights.qiagen.com/products-overview/) was completed using all annotated genes and non-coding RNA with changed levels of RNA in impaired WM compared to intact WM. The analysis settings were: only proven direct interactions in either direction as recorded in the Ingenuity Knowledge Base (Genes Only) that have been experimentally observed in human, rat or mouse tissue; the Core Analyses software was allowed to allocate genes automatically into classifications according to their known functions. Fisher's right tailed exact test and the –log(p-value) was then used to identify pathways where there was a significant over representation of genes beyond what would be expected by a random allocation of differentially expressed genes.

An analysis of all annotated genes and non-coding RNA was completed using IPA Pathway Explorer to identify gene expression interactomes that included genes differentially expressed between impaired WM and intact WM. To exclude weak interactions settings were Direction: any, Data Sources: Ingenuity Expert Information only, Confidence Level: experimental observed and Species: human, mouse and rat using a Stringent Filter and no interactions involving intermediary genes. Mutations were included and all types of relationships allowed.

By limiting analyses to the Ingenuity Expert Information Database, all interactions would have been published in what IPA consider high-ranking journals and the data relating to each gene would have undergone manual curation of the full text of each publication to establish contextual details.

Data Availability

Data files are currently held by the CRC for Mental Health and will be made available to bona fide researchers upon request.

Results

Cluster analyses

The Letter Number Span and Digit Span backwards data analyses using Akaike's Information Criterion with Euclidean distance showed that a 2-group solution best described the data collected from 34 patients with schizophrenia. Hierarchical agglomerative clustering, with Ward's minimum variance method and Squared Euclidean distance, was used to confirm the number of cluster subgroups, and which patients fitted into each group (Figure 1). Hence, despite relatively small numbers, the two subgroups consisted of patients with impaired WM (n = 16) and those with intact WM (n = 18) (Table 1).

There were no significant differences in age, years of education, gender ratios, frequency of smoking, depression severity (MADRS), severity of psychopathology (PANSS), age at diagnosis, duration of illness, age at first reported illness, or premorbid level of intellect (WTAR) between impaired WM and intact WM (Table 1). As would be expected, scores from

Letter Number Span and Digit Span Backward were significantly lower in impaired WM. In addition, the patients in the impaired WM group were being treated with lower levels of antipsychotic drugs compared to those with intact WM. However, the frequency in which different drugs were prescribed did not differ significantly between impaired WM and intact WM (Table 1).

Gene Expression: Working Memory Phenotypes within Schizophrenia

Levels of RNA for 17,612 genes and non-coding RNA were detectable in blood from patients with impaired WM and intact WM with RNA for 72 genes being higher in impaired WM (fold impaired WM / intact WM: Figure 1; Table 2). There were no genes with lower expression when comparing data from impaired WM and intact WM.

We wished to determine if the changes in gene expression we identified comparing impaired WM to those from intact WM differed from what has been reported at the level of schizophrenia. Thus, we reviewed the literature to determine which of the 72 genes differentially expressed between impaired WM and intact WM had previously been identified in studies comparing schizophrenia to healthy controls. Other studies have reported high levels of RNA for *FAM54A* (Gebicke-Haerter et al., 2021) as well as lower levels of *IQSEC*3 (Ellis et al., 2016) and *PRUNE2* (Scarr et al., 2018a) in postmortem CNS from patients with schizophrenia. Proteomic studies have reported PMP2 to be lower in patients with schizophrenia (Pinacho et al., 2016) and that whilst levels of ZNF540 protein was not altered, it was differentially phosphorylated in those with the disorder (Saia-Cereda et al., 2016). Using white blood cells, increased levels of *ATP13A5* RNA was reported in schizophrenia (Glatt et

al., 2011) whilst proteomic studies, using serum or plasma, have reported higher levels of CCL11 (Teixeira et al., 2008) and CCL26 (Sun et al., 2015) in people with the disorder.

Next, we completed an IPA core analyses which showed canonical pathways involved in influenza virus infection and immunity would be affected by changes in gene expression in the impaired WM (Table 3). At the level of diseases and bio functions the changes in gene expression in impaired WM were not readily associated with disorders of the CNS. Changes in gene expression at the level of molecular and cellular function were predicted to affect Cellular Growth, Cellular Proliferation, Cellular Movement, Cell Death and Survival, Cellular Compromise and Cell Cycling. At the level of physiological development and function, the changes in gene expression would affect a number of processes, two of which would impact on immunity.

Pathway Explorer did not show gene expression interactomes containing genes with altered levels of expression in patients with impaired WM.

Discussion

This study is the first to identify of two clusters (impaired WM and intact WM) within schizophrenia based on differences in working memory performance. This discovery extends our previous research demonstrating the utility of data driven cognitive clustering to define more homogeneous phenotypes within the diagnosis of schizophrenia (Carruthers et al., 2019; Green et al., 2020). An important component of this study was the use of a transcriptomic technology to show there was an increase in expression of 72 genes in the blood of people with impaired WM compared to intact WM. Notably, published data suggests changed levels of

expression and / or translation for 8 of these genes (11.4 %) is detectable at the level of the syndrome of schizophrenia. This low commonality between changed gene expression and / or translation between our working memory sub-groups compared to schizophrenia as a whole is similar to findings in the CNS of a sub-group within schizophrenia characterised by a marked loss of cortical muscarinic M1 receptors (Dean and Scarr, 2020). Moreover, this study is adding support to the hypothesis that there will be unique changes in biological mechanisms in sub-groups within the syndrome of schizophrenia and understanding the consequences of these changes will increase understanding of the molecular pathology of the disorder as a whole (Tamminga et al., 2017). With regards to understanding the consequences of changes in gene expression between impaired WM and intact WM, our Core Analyses of changed gene expression indicated that immune pathway activity would differ between the sub-groups. This finding is consistent with a previous study comparing gene expression between patients with schizophrenia and controls, which also suggested immune / inflammatory mechanisms were linked to the verbal working deficits (Ukkola-Vuoti et al., 2019).

Focussing on the known functions of the genes with changed levels of expression between our working memory sub-groups, there was a higher level of expression of the RAS-like, estrogen-regulated, growth inhibitor (RERG) gene in impaired WM; this is significant as genetic variation in that gene has been reported to be associated with the level of cognitive ability in humans (Davies et al., 2018). Unfortunately, our sample size does not allow us to determine if patients in impaired WM have an over-representation of the risk genotype for poorer cognitive functioning. However, detecting changes in the expression RERG raises the possibility that there is a genetic component and that impaired WM / intact WM could be cognitive endophenotypes within schizophrenia. In addition, there were higher levels of expression for the gene neuropilin (NRP) and tolloid (TLL)-like 1 (NETO1) in impaired WM.

This is also a noteworthy as that gene is known to have a critical role in spatial learning and memory by regulating synaptic N-methyl-D-aspartic acid receptor (NMDAR) complexes (Ng et al., 2009), suggesting changes in glutamatergic activity may be present in those with impaired WM.

There were higher levels of expression for 9 olfactory receptors in the blood from impaired WM; in the CNS these receptors have a critical role in olfaction (Fleischer et al., 2009). This suggests there may be some connection between peripheral gene expression in impaired WM patients and CNS function, as it is known that olfaction is affected in patients with schizophrenia before treatment with antipsychotic drugs (Brewer et al., 2001). In addition, changes in peripheral expression of olfactory receptors could be potential markers of a deficit in working memory, as deficits in olfaction are present in people at high risk of developing schizophrenia (Takahashi et al., 2000). The family 8, subfamily S, member 1 (OR8S1) and olfactory receptor, family 9, subfamily Q, member 1 (OR8Q1) have both been implicated in olfactory cognition (Ignatieva et al., 2014). Whilst the link between cognition and changes in level of olfactory receptor expression in blood may seem tenuous, it has been shown that there are lower levels of expression of olfactory receptors in blood after a traumatic brain injury (Zhao et al., 2013). This raises the possibility that olfactory receptors may be among the genes where there are correlations between levels of blood and CNS expression (Sullivan et al., 2006). If this were true, the changes in olfactory receptor gene expression we report in the blood of patients with impaired WM could be present in their CNS.

It is known that control of energy and metabolism is critical to maintaining cognitive function. Therefore, it is of note that our study has shown changes in expression levels of adenylate kinase 7 (AK7) and the apelin receptor (APLNR) as these genes are involved in metabolic

pathways. AK7 is one of a number of adenylate kinases that are now recognised as having significant roles in cellular energetics and metabolic sensing (Zhang et al., 2014). Like AK7, APLNR has a number of critical roles, one of which is the regulation of energy metabolism (Chapman et al., 2014). Our findings raise the possibility that if changes in levels of expression of two such important energy regulating genes are present in the CNS in impaired WM, deficiencies in energy availability could be contributing to their working memory deficits (Kapogiannis and Mattson, 2011).

There were higher levels of expression for C1q and tumour necrosis factor related protein 7 (C1QTNF7), chemokine (C-C motif) ligand 11 (CCL11), chemokine (C-C motif) ligand 26 (CCL26), interferon α2 (IFNA2), interferon, α7 (IFNA7), inhibin α (INHA) and UL16 binding protein 1 (ULBP1), all of which are involved in inflammation and immunity (Berjaoui et al., 2015; López de Padilla and Niewold, 2016; Nagineni et al., 2015; Phillips et al., 2009; Vakkila and Lotze, 2004). This is of interest because systemic inflammation has previously been associated with working memory deficits (Skelly et al., 2019). Notably, other studies using gene expression microarrays have associated increased immune system and inflammation with poorer cognitive performance in schizophrenia (Ukkola-Vuoti et al., 2019; Wu et al., 2016; Zheutlin et al., 2016).

At this point it is not possible to determine if the changes in gene expression in our working memory sub-groups would be mirrored in the CNS because cases in postmortem CNS collections cannot be accurately sub-divided according to WM capability. However, one study has reported detecting the same changes in the expression of a limited number of genes in the periphery and CNS of patients with schizophrenia (Glatt et al., 2005). Thus, it could be possible to investigate if there are changes in CNS gene expression between working memory sub-

groups if tissue was collected prospectively from patients with schizophrenia who had be allocated to the sub-groups prior to death (Deep-Soboslay et al., 2011).

Study Limitations

This study has a number of limitations which include small cohort sizes, not replicating findings using qPCR and possible impacts of drug treatments which together mean our data are preliminary and need replicating in larger cohorts. In acknowledging these limitations, we also note that we have repeatedly shown that data obtained using similar cohort sizes and, using exactly the same approach accept that RNA was extracted from CNS, has given results that inform on the impact of changes in gene expression on the underlying biology of the disorder (Scarr et al., 2016; Tang et al., 2012; Torkamani et al., 2010; Udawela et al., 2015). Hence, even our preliminary data is a significant new addition to existing data on the potential breakdown of biochemical homeostasis of sub-groups within schizophrenia. Although it was not possible to validate our expression data using qPCR (due to loss of duplicate samples after a freezer breakdown) we have replicated changes in gene expression measured using Affymetrix™ Human Exon 1.0 ST Array with qPCR repeatedly in our CNS studies (Narayan et al., 2008; Scarr et al., 2016; Scarr et al., 2018b; Udawela et al., 2015). This strongly argues that our data on gene expression in this study are valid and interpretable. As with any study that does not use drug naïve patients, ongoing treatment could be a confound. However, unlike studies comparing non-drug naïve patients to controls, our data would be much less affected by the confound of antipsychotic drug treatment as both impaired WM and intact WM had been treated with these drugs even though the doses of antipsychotic drugs received by the impaired WM were lower than those for the intact WM.

It has long been considered that biochemical changes associated with schizophrenia extend beyond the CNS and could be used to gain insight into how such changes could affect CNS function (Asor and Ben-Shachar, 2012), could identify abnormalities in peripheral mechanisms relevant to CNS functions (Dean et al., 1992a) or identify neuro-active molecules that have yet to be identified in the CNS (Dean et al., 1992b). However, as it is now clear that the biological role of the same gene in the periphery and CNS can have marked differences (Dean, 2011), caution must be exercised in overly extrapolating data from peripheral gene expression in sub-groups within the syndrome of schizophrenia. Given that proviso, studies on peripheral gene expression in defined sub-groups within schizophrenia can be used to further the hypothesis that understanding their biological basis will give valuable insight into the complex molecular pathology of such a complex disorder (Tamminga et al., 2017). In addition, such studies can contribute to the search for biomarkers for sub-groups within the syndrome of schizophrenia that could allow the delivery of more personalised medicine to aid in improving clinical outcomes (Aberg et al., 2014; Scarr et al., 2015; Tamminga et al., 2017; Tomasik et al., 2012).

Conclusions

Our preliminary data gives more support to the hypothesis that studying phenotypes within the syndrome of schizophrenia has the potential to give valuable new data on the underlying pathophysiology of the disorder. In the case of impaired WM it is particularly notable that there are changes in levels of expression of genes that can be directly linked to the regulation of cognition (Figure 3). These changes in gene expression suggest that inherited changes *RERG* as well as changes in glutamate activity, olfaction, regulation of energy utilisation and / or inflammation may be particularly affected in patients with impaired WM. Although preliminary, our data raises the possibility that a larger study could show that the specific

changes in gene expression we have identified could prove to be the biomarkers needed to develop a blood test to identify those with impaired WM. Such a test would aid clinical decision making relating to the delivery of personalised medicine directed toward improving the working memory suffered by patients within the impaired WM sub-group (Gilleen et al., 2021; Lett et al., 2014; Papazova et al., 2018).

Acknowledgements

The authors would like to acknowledge Dr. Madhara Udawela for the technical assistance she provided in extracting RNA from blood for this study and funding from the Cooperative Research Centre for Mental Health that supported part of this study. The authors wish to acknowledge the contributions of study participants, staff at recruitment services, staff at the Centre for Mental Health, and staff at the Monash Alfred Psychiatry Research Centre, including Professor Jayashri Kulkarni. The authors acknowledge the support of the Victorian Government's Operational Infrastructure Support Programme. Participants for this study were sourced, in part, through the Cognitive and Genetic Explanations of Mental Illness (CAGEMIS) bio-databank, which is supported by the Australian National Health and Medical Research Council (NHMRC) project grant (GNT1060664 to SLR) and fellowships (GNT1154651 to SLR, GNT546262 to CG, GNT1142424 to EJT and GNT1088785 to TVR). EHXT was supported by an Australian Postgraduate Award at Monash University. KB is supported by an E.H Flack Fellowship. This study was funded in part by the Cooperative Research Centre for Mental Health. SR and TVR received funding from Australian Rotary Health/Bipolar Expedition and the Helen McPherson Smith Trust. CG received funding from the Rebecca Cooper Foundation.

Authors Contribution

BD, ES, SS and CG conceptualised the study. ET, ET, TvR, EN, PS and SC contributed to participant recruitment. KB managed blood sample processing and storage. BD and ES analysed the transcriptomic data. BD wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

Competing Interests

The authors have no competing interests to report.

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Figures Legends

Figure 1: A dendrogram of Hierarchical agglomerative clustering showing the two distinct cluster solution that best fitted data from the Letter Number Span and Digit Span Backward tests.

Figure 2: Volcano plots showing the levels of RNA, expressed as a fold change between patients with and without working memory deficits (impaired WM / intact WM) in comparison to the significance of change in levels of expression calculated using t-tests. Genes with higher levels RNA in blood from patients with impaired WM are shown as green dots.

Figure 3: Schematic outlining genes with high levels of expression in the blood from patients with working memory deficits that could affect cognition though heritability, glutamate, olfaction, energy and metabolism or immunity and inflammation.

Figure 1

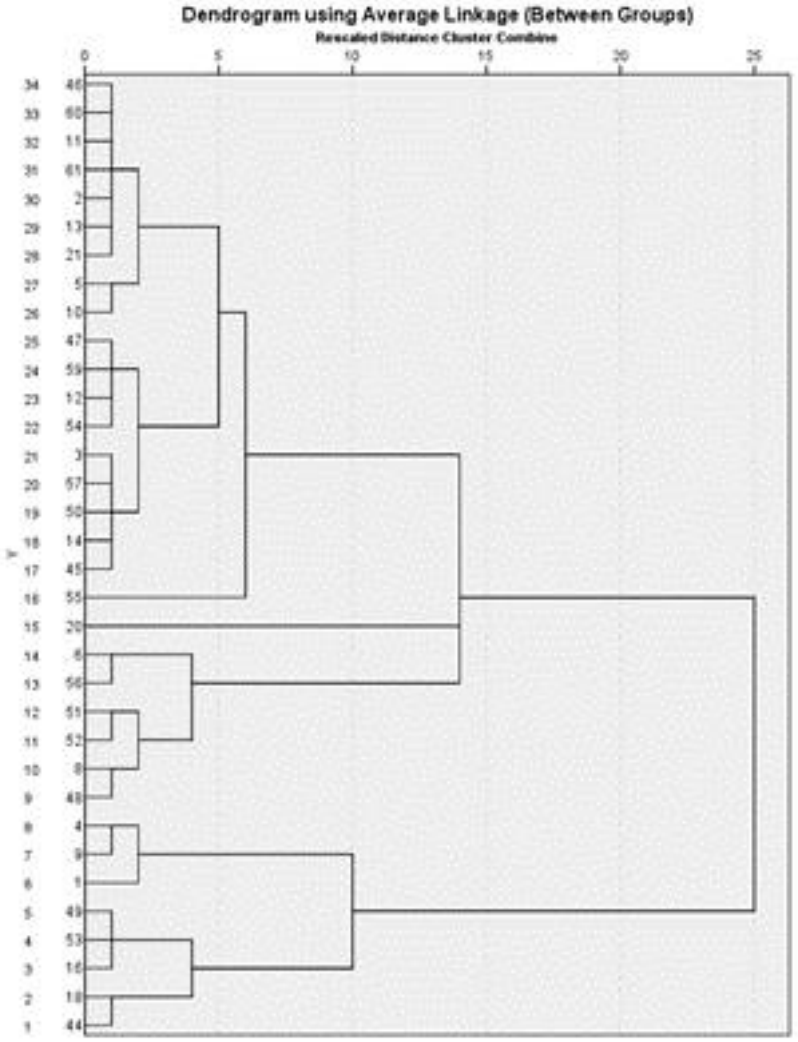

Dendrogram using Average Linkage (Between Groups)
Rescaled Distance Cluster Combine
0
5
10
15
20
25

Figure 2

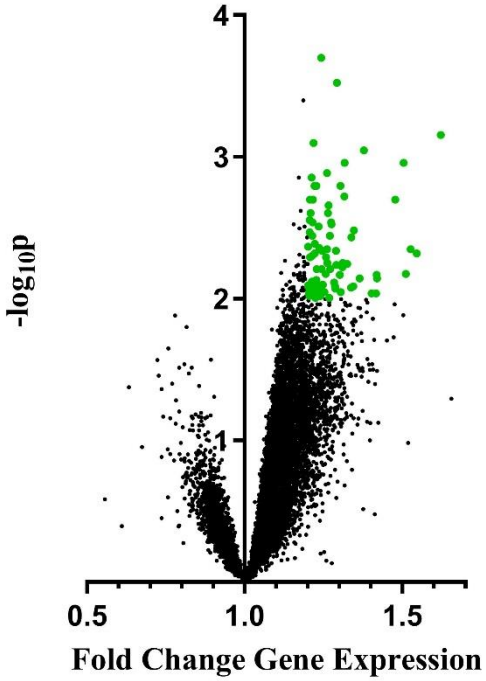


Figure 3

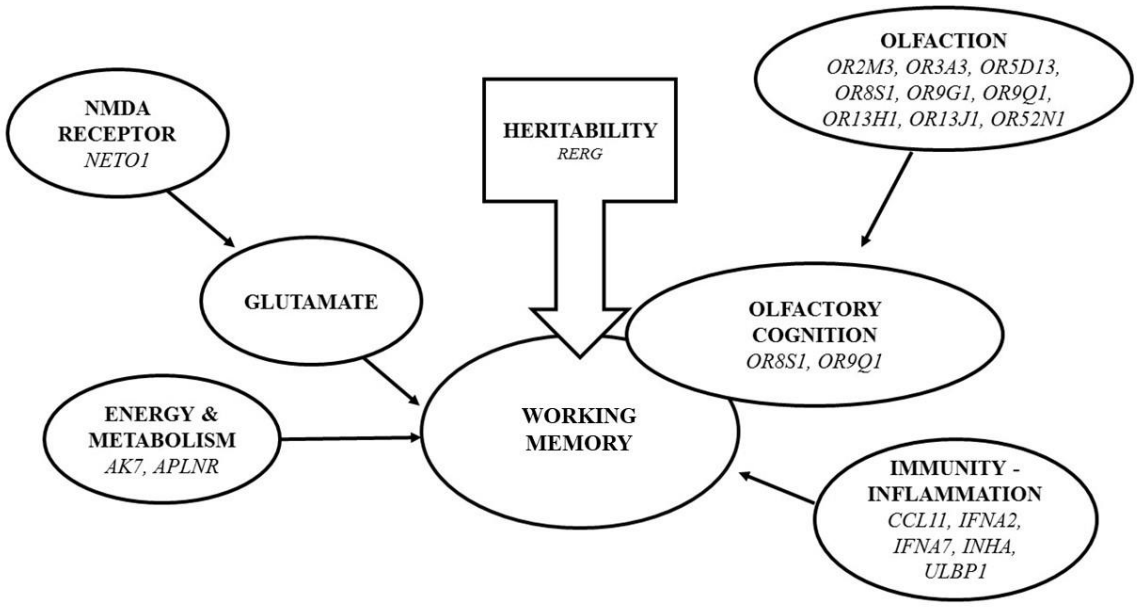

NMDA RECEPTOR
NETO1
HERITABILITY
RERG
OLFACTION
OR2M3, OR3A3, OR5D13, OR8S1, OR9G1, OR9Q1, OR13H1, OR13J1, OR52N1
GLUTAMATE
OLFACTORY COGNITION
OR8S1, OR9Q1
ENERGY & METABOLISM
AK7, APLNR
WORKING MEMORY
IMMUNITY - INFLAMMATION
CCL11, IFNA2, IFNA7, INHA, ULBP1

Table 1: Demographic, clinical, cognitive variables (where appropriate expressed as mean ± SEM) and antipsychotic drugs used in treatment relevant to cases in this study.

		Working Memory Phenotypes			
		Impaired	**Intact**	**t or χ^2**	**p**
Demographics	n	16	18		
	Age	42 ± 2.2	42 ± 2.7	0.006	0.99
	Years of education	14 ± 1.5	14 ± 0.7	0.07	0.94
	Gender (male / female)	10 / 6	10 / 8	0.16	0.68
	Smoking: Yes / No / Unknown	6 / 8 / 2	7 / 11 / 0	2.44	0.30
Clinical	MADRS	8.21 ± 1.89	8.30 ± 2.07	0.28	0.78
	PANSS	57 ± 5.56	57 ± 3.0	0.09	0.93
	Age at diagnosis	25 ± 1.87	26 ± 2.30	0.11	0.91
	Duration of illness	16 ± 3.01	17 ± 2.84	0.23	0.82
	Age at first self-reported symptoms	23 ± 1.89	21 ± 2.88	1.33	0.19
	Antipsychotic Drug Dose†	300 ± 100	720 ± 100	2.78	**0.01**
Cognitive	WTAR Raw Score	37 ± 2.6	40 ± 1.7	0.84	0.41
	Letter Number Span	11 ± 0.05	16 ± 0.62	6.67	**<0.0001**
	Digit Span Backwards	4.38 ± 0.41	7.1 ± 0.37	4.99	**<0.0001**
Antipsychotic Drugs	Clozapine	3	5	6.52	0.69
	Seroquel	2	5		
	Aripiprazole	2	1		
	Olanzapine	1	1		
	Paliperidone	1	1		
	Risperidone	1			
	Zuclopenthixol	1			
	Flupentixol		1		
	Amisulpride		1		
	Missing	5	3		

† Antipsychotic drug dose expressed as chlorpromazine equivalents

Abbreviations: MADRS = Montgomery-Aberg Depression Rating Scale, PANSS = Positive and Negative Symptom Scale, WTAR = Wechsler Test of Adult Reading.

Table 2: Genes (ranked by fold change in RNA) with altered levels of RNA in blood from patients schizophrenia and impaired working memory compared to those with intact working memory.

Gene Name	Gene Symbol	Chromosome	Fold	p
pregnancy specific beta-1-glycoprotein 6	PSG6	19q13.2	1.62	<0.001
ankyrin repeat and GTPase domain Arf GTPase activating protein 11	AGAP11	10q23.2	1.53	0.005
nascent polypeptide-associated complex alpha subunit 2	NACA2	17q23.2	1.51	0.007
olfactory receptor, family 9, subfamily G, member 1	OR9G1	11q12.1	1.50	0.001
interferon, alpha 7	IFNA7	9p22	1.48	0.002
olfactory receptor, family 9, subfamily Q, member 1	OR9Q1	11q12.1	1.42	0.007
phosphoribosyl pyrophosphate synthetase 1-like 1	PRPS1L1	7p21.1	1.40	0.009
family with sequence similarity 54, member A	FAM54A	6q23.3	1.38	<0.001
ribosomal protein L41	RPL41	12q13	1.36	0.007
olfactory receptor, family 2, subfamily M, member 3	OR2M3	1q44	1.35	0.003
UL16 binding protein 1	ULBP1	6q25	1.34	0.008
BEN domain containing 6	BEND6	6p12.1	1.34	0.008
olfactory receptor, family 5, subfamily D, member 13	OR5D13	11q11	1.32	0.006
long intergenic non-protein coding RNA 1951	LINC01951	5q35.2	1.32	0.001
ATPase type 13A5	ATP13A5	3q29	1.32	0.002
interferon, alpha 2	IFNA2	9p22	1.31	0.006
chondrosarcoma associated gene 1	CSAG1	Xq28	1.30	0.009
tubulin, alpha 3c	TUBA3C	13q11	1.29	<0.001
olfactory receptor, family 13, subfamily J, member 1	OR13J1	9p13.3	1.29	0.006
long intergenic non-protein coding RNA 1555	LINC01555	1p22.3	1.29	0.005
HEXA antisense RNA 1	HEXA-AS1	15q23	1.29	0.009
long intergenic non-protein coding RNA 652	LINC00652	20p11.23	1.28	0.003
F-box protein 16	FBXO16	8p21.1	1.27	0.003
peripheral myelin protein 2	PMP2	8q21.3-q22.1	1.27	0.006
IQ motif and Sec7 domain 3	IQSEC3	12p13.33	1.27	0.004
achaete-scute complex homolog 3 (Drosophila)	ASCL3	11p15.3	1.27	0.009
melanoma antigen family B, 2	MAGEB2	Xp21.3	1.27	0.002
breakpoint cluster region	BCR	22q11|22q11.23	1.26	0.003
RAN binding protein 17	RANBP17	5q34	1.26	0.006
shisa homolog 7 (Xenopus laevis)	SHISA7	19q13.42	1.26	0.005
heat shock 22kDa protein 8	HSPB8	12q24.23	1.26	0.001
transmembrane protein 31	TMEM31	Xq22.2	1.26	0.005
prune homolog 2 (Drosophila)	PRUNE2	9q21.2	1.26	0.007
neuropeptide VF precursor	NPVF	7p21-p15	1.25	0.009
family with sequence similarity 47, member B	FAM47B	Xp21.1	1.25	0.008
adenylate kinase 7	AK7	14q32.2	1.25	0.008
PDZ domain containing 1	PDZK1	1q21	1.25	0.005
forkhead box B1	FOXB1	15q22	1.24	0.006
inhibin, alpha	INHA	2q33-q36	1.24	<0.001
dermcidin	DCD	12q13.1	1.24	0.009
protein phosphatase 1 regulatory subunit 36	PPP1R36	14q23.3	1.24	0.009
olfactory receptor, family 8, subfamily S, member 1	OR8S1	12q13.11	1.24	0.004
chromosome 11 open reading frame 42	C11orf42	11p15.4	1.24	0.003
chemokine (C-C motif) ligand 11	CCL11	17q21.1-q21.2	1.23	0.006
C1q and tumor necrosis factor related protein 7	C1QTNF7	4p15.3	1.23	0.002
neuropilin (NRP) and tolloid (TLL)-like 1	NETO1	18q22.2	1.23	0.007
membrane-associated ring finger (C3HC4) 10	MARCH10	17q23.2	1.22	0.009
olfactory receptor, family 13, subfamily H, member 1	OR13H1	Xq26.2	1.22	0.008
keratin 28	KRT28	17q21.2	1.22	0.004
lengsin, lens protein with glutamine synthetase domain	LGSN	6pter-q22.33	1.22	0.005
5-hydroxytryptamine (serotonin) receptor 2C	HTR2C	Xq24	1.22	0.008
cysteine and glycine-rich protein 2	CSRP2	12q21.1	1.22	0.002
retinal pigment epithelium-specific protein 65kDa	RPE65	1p31	1.22	0.009
WT1 antisense RNA (non-protein coding)	WT1-AS	11p13	1.22	<0.001
crystallin, gamma C	CRYGC	2q33-q35	1.22	0.002
olfactory receptor, family 3, subfamily A, member 3	OR3A3	17p13.3	1.22	0.003
olfactory receptor, family 52, subfamily N, member 1	OR52N1	11p15.4	1.21	0.004
tissue factor pathway inhibitor 2	TFPI2	7q22	1.21	0.008
FLJ42102 protein	FLJ42102	11q13.4	1.21	0.008
long intergenic non-protein coding RNA 1949	LINC01949	5q14.3	1.21	0.009
apelin receptor	APLNR	11q12	1.21	0.001
chromosome 11 open reading frame 88	C11orf88	11q23.1	1.21	0.009
ankyrin repeat and sterile alpha motif domain containing 4B	ANKS4B	16p12.2	1.21	0.003
zinc finger protein 540	ZNF540	19q13.12	1.21	0.002
chemokine (C-C motif) ligand 26	CCL26	7q11.23	1.21	0.005
zymogen granule protein 16 homolog (rat)	ZG16	16p11.2	1.21	0.003
long intergenic non-protein coding RNA 1869	LINC01869	19q13.33	1.21	0.003
FRAS1 related extracellular matrix protein 2	FREM2	13q13.3	1.21	0.009
RAS-like, estrogen-regulated, growth inhibitor	RERG	12p12.3	1.21	0.008
family with sequence similarity 177, member B	FAM177B	1q41	1.21	0.009

long intergenic non-protein coding RNA 1114	LINC01114	21q22.2	1.21	0.008
DDB1 and CUL4 associated factor 4-like 2	DCAF4L2	8q21.3	1.21	0.004

Table 3: IPA Core Analysis of genes that were differentially expressed in schizophrenia with impaired working memory compared to those with intact working memory.

Top Canonical Pathways		
Name	p-value	Overlap
Role of lipids / lipids rafts in the pathogenesis of influenza	2.06E-03	8.7% 2/23
Role of hypercytokemmia / hyperchemokinemia in the pathogenesis of influenza	7.08E-03	4.7% 2/43
Role of RIG1-like receptors in antiviral innate immunity	7.40E-03	4.5% 2/44
Role of cytokines in mediating communication between immune cells	1.10E-02	3.7% 2/54
Phosphoribosyl diphosphate (PRPP) biosynthesis 1	1.17E-02	25% 1/4
Top Diseases and Bio Functions	p value range	# molecules
Cancer		
Endocrine Systems Disorders	4.92E-02 - 4.43E-04	14
Organismal Injury and Abnormalities	4.87E-02 - 4.43E-04	9
Reproductive System Disease	4.92E-02 - 4.43E-04	19
Hypersensitivity Response	4.87E-02 - 4.43E-04	10
	4.59E-02 - 6.47E-04	3
Molecular and Cellular Functions		
Cellular Growth and Proliferation	4.87E-02 - 6.47E-04	6
Cellular Movement	4.59E-02 - 6.47E-04	4
Cell Death and Survival	4.87E-02 - 1.12E-03	7
Cellular Compromise	8.77E-03 - 1.12E-03	4
Cell Cycle	4.87E-02 - 2.93E-03	3
Physiological Systems Development and Function		
Organismal Functions	2.85E-01 - 8.26E-03	2
Haematological System Development and Function	4.87E-02 - 6.47E-04	6
Immune Cell Trafficking	4.71E-02 - 6.47E-04	5
Cell-mediated Immune Response	2.90E-02 - 2.93E-03	2
Embryonic Development	4.03E-02 - 2.93E-03	5