quantitative real-time PCR. In this report, we describe a novel strategy to study disease-associated molecular profiles in a neuronal cell population by combining nasal biopsy and laser-captured microdissection to enrich OE neuronal layers. We also show that the enriched OE neuronal layer is a good resource for identifying molecular profile changes that could facilitate the discovery of biomarkers. We note that non-neuronal sustentacular cells may still be present with this method of dissection. This limitation could be easily overcome by combining histological approaches, such as immunohistochemistry and *in situ* hybridization. Odor identification deficits examined in this study might reflect abnormalities of both peripheral and central olfactory circuitry. Instead, odor-specific detection threshold sensitivity, which reflects abnormalities in the peripheral components of the olfactory system, especially OE, could be a more useful index of odor function to correlate with gene expression profiles in future studies.[10] One caution that usually applies to all research in the field of mental illnesses, especially schizophrenia, is the use of samples from patients with chronic medication. Thus, it will then be important to study first-onset patients and extend the research to their non-affected first-degree relatives to overcome the effect of medications on gene expression. This methodology may be useful to follow up patients in order to identify biomarkers of treatment response. This can also be applied to individuals at risk in order to predict passage to a full-blown psychosis. Finally, we hope to develop various biomarkers that can be tested during a simple clinical examination and reflect etiology-based mechanisms of disease susceptibility and pathology.

Conflict of interest

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Variation in *DISC1* is associated with anxiety, depression and emotional stability in elderly women

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A recent association study identified three single nucleotide polymorphisms (SNPs) (rs1538979, rs821577 and rs821633) in *Disrupted in Schizophrenia 1* (*DISC1*) gene that, either independently or in combination, influence risk of schizophrenia and bipolar disorder.[1] We investigated the association between these SNPs and the personality trait emotional stability/neuroticism (a potential endophenotype for mental illness), and anxiety and depression in two relatively healthy older Scottish cohorts (Lothian Birth Cohort of 1921 (LBC1921),[2] $n = 360$; and Lothian Birth Cohort of 1936 (LBC1936),[3] $n = 1065$).

Personality was assessed at a mean age of ~81 years (LBC1921) or ~70 years (LBC1936). Emotional stability was measured using the IPIP Big-Five 50-item inventory[4] and, for LBC1936 only, neuroticism was assessed using the NEO five-factor inventory.[5] Mood was assessed at a mean age of ~79 years (LBC1921) or ~70 years (LBC1936) using scores on the Hospital Anxiety and Depression scale (HADS).[6] LBC1921 was genotyped on a Sequenom platform (Sequenom, San Diego, CA, USA)[1] and LBC1936 using TaqMan (Applied Biosystems, Pleasonton, CA, USA) at

Table 1 Effect of each SNP/SNP interplay on HADS anxiety and depression scores, IPIP emotional stability scores and NEO Neuroticism scores (LBC1936 only) for LBC1921 and LBC1936, and for a joint analysis of LBC1921 and LBC1936.

		HADS anxiety			*HADS depression*			*Emotional stability*			*Neuroticism*
		LBC1921	*LBC1936*	*Joint*	*LBC1921*	*LBC1936*	*Joint*	*LBC1921*	*LBC1936*	*Joint*	*LBC1936*
rs1538979 risk allele	Combined	0.853	0.198	0.426	0.36	0.649	0.538	0.705	0.823	0.813	0.664
carrier versus all others	Male	0.875	0.513	0.660	0.795	0.816	0.902	0.323	0.791	0.294	0.814
	Female	0.915	0.250	0.471	0.244	0.672	0.397	**0.045**	0.963	0.084	0.698
rs821577 risk allele	Combined	0.542	0.073	0.154	0.104	0.192	**0.034**	0.229	0.434	0.139	0.394
carrier versus all others	Male	0.299	0.757	0.423	0.259	0.678	0.237	0.836	0.694	0.986	0.650
	Female	**0.044**	**0.033**	**0.004**	0.229	0.139	0.060	0.099	0.126	**0.024**	0.077
rs821633 risk allele	Combined	0.538	0.701	0.715	0.925	0.673	0.903	0.817	0.390	0.531	0.260
carrier versus all others	Male	0.776	0.067	0.558	0.128	0.899	0.206	0.918	0.995	0.924	0.992
	Female	0.539	0.270	0.264	0.066	0.443	0.185	0.811	0.215	0.393	0.097
All three risk alleles	Combined	0.692	0.218	0.823	0.409	0.858	0.396	0.282	0.760	0.398	0.736
versus all others	Male	0.876	0.316	0.570	0.775	0.764	0.701	0.710	0.218	0.859	0.645
	Female	0.377	0.449	0.746	0.299	0.946	0.359	0.173	0.393	0.097	0.996
rs821633 in absence of	Combined	0.635	0.209	0.296	0.387	0.519	0.269	0.731	0.745	0.872	0.397
other risk alleles versus	Male	0.079	0.637	0.072	0.505	0.882	0.518	0.224	0.928	0.240	0.497
all others	Female	0.260	0.191	0.744	0.570	0.407	0.343	**0.046**	0.701	0.103	0.615
rs821577 and rs821633	Combined	0.844	0.665	0.976	0.422	0.428	0.265	0.516	0.248	0.251	0.230
risk alleles versus all	Male	0.121	**0.029**	**0.016**	0.370	0.721	0.536	0.658	0.680	0.546	0.520
others	Female	0.061	0.188	**0.021**	**0.032**	0.434	**0.015**	0.127	**0.038**	**0.015**	**0.013**

Abbreviations: HADS, Hospital Anxiety and Depression scale; LCB, Lothian Birth Cohort; SNP, single nucleotide polymorphism.
Main effect *P*-values are shown with *P*-values <0.05 indicated in bold.

the Wellcome Trust Clinical Research Facility, Edinburgh. Genotype frequencies did not differ significantly from the Hardy–Weinberg equilibrium ($P>0.01$) and were LBC1921 (LBC1936); rs1538979, C/C = 262 (749); T/C = 80 (230); T/T = 10 (29), rs821577, G/G = 61 (193); G/T = 163 (492); T/T = 118 (351) and rs821633, C/C = 35 (94); C/T = 128 (429); T/T = 175 (483). Phenotypic outliers with *z*-scores greater than ± 3 were removed before analyses. Descriptive statistics of the phenotypic variables are listed in the Supplementary Table. General linear modelling was performed in SPSS v13 (SPSSinc, Chicago, IL, USA) using carrier status (as defined in Hennah *et al.* (2008)[1]) for each SNP or combination of SNPs and sex as fixed factors. As previous studies have shown that variance in *DISC1* has stronger effects in females than in males,[1] the models were also run analysing males and females separately. LBC1921 and LBC1936 were first analysed separately and then, for HADS and emotional stability, combined analyses were performed with cohort added to the models as a fixed factor.

In LBC1921, female carriers of the rs821577 risk allele had significantly higher HADS anxiety scores than did non-carriers ($P=0.044$, $\eta^2=0.021$). This association was replicated in LBC1936 ($P=0.033$, $\eta^2=0.009$), and became more significant when data from the two cohorts were combined ($P=0.004$, $\eta^2=0.0012$) (Table 1). In the combined analysis, male carriers of both the rs821577 and rs821633 risk alleles had significantly lower HADS anxiety scores ($P=0.016$, $\eta^2=0.009$). Female carriers of the risk alleles had significantly higher HADS anxiety scores ($P=0.021$, $\eta^2=0.008$). LBC1921 participants who were $\sim$9 years older than LBC1936 had significantly higher HADS depression scores ($P<0.05$ for all models). This is likely to be partly owing to them being in poorer health because of being older. In LBC1921, female carriers of both the rs821577 and rs821633 risk alleles had higher HADS depression scores than did non-carriers ($P=0.032$, $\eta^2=0.024$). This was not replicated in LBC1936 ($P=0.434$), but was significant in a combined analysis of both cohorts ($P=0.015$, $\eta^2=0.009$) (Table 1). In LBC1936, IPIP emotional stability scores and NEO neuroticism scores were highly inversely correlated ($r=-0.76$, $n=939$, $P<0.001$). In the combined cohort analysis, female carriers of the rs821577 risk allele had lower emotional stability scores than did non-carriers ($P=0.024$, $\eta^2=0.008$). In LBC1936, female carriers of both the rs821577 and rs821633 risk alleles had significantly lower emotional stability ($P=0.038$, $\eta^2=0.010$) and higher neuroticism ($P=0.013$, $\eta^2=0.014$) scores than did non-carriers. In the combined cohort analysis, female carriers of these two risk alleles had significantly lower emotional stability scores ($P=0.015$, $\eta^2=0.010$).

We have shown that rs821577, either independently or in the presence of the risk allele for SNP rs821633, is associated with increased anxiety and depression and with higher levels of neuroticism,

in women, in two cohorts of older normal individuals. These risk alleles have previously been associated with schizophrenia, bipolar disorder, and social and physical anhedonia, mainly in females.[1,7] Reports suggest that heritability of neuroticism, anxiety and depression is higher in females than in males, and that the genes involved differ between men and women.[8–10] We tested SNPs and models specifically chosen on the basis of earlier evidence, and hence do not believe that stringent multiple testing corrections are appropriate, but these results need to be replicated in other suitable cohorts before variation in *DISC1* is fully accepted as contributing to normal variation in neuroticism and mood.

Conflict of interest

The authors declare no conflict of interest.

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Renalase, a novel soluble FAD-dependent protein, is synthesized in the brain and peripheral nerves

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In the central nervous system (CNS), the oxidative deamination of monoamine neurotransmitters is accomplished by two membrane-bound enzymes: monoamine oxidase (of which there are two isoforms, MAO-A and MAO-B) and semicarbazide-sensitive amine oxidase (SSAO). The combined activities of these proteins are crucial for the regulation of neurotransmitter disposition and, consequently, normal brain function. It is therefore not surprising that MAO-A and B gene polymorphisms and altered expression are implicated in a variety of neurological disorders.[1–5] Moreover, the demonstration that MAO inhibitors, such as iproniazid, were effective antidepressant agents was pivotal in Schildkraut's[6] formulation of the catecholamine hypothesis of affective disorders. Here, we report for the first time the identification of a novel flavin adenine dinucleotide (FAD)-dependent protein, renalase, in various regions of the CNS. We show that the renalase gene is expressed in the hypothalamus and peripheral nerves. Furthermore, we reveal the existence of several splice variants of the renalase gene, which potentially serve to further regulate levels of monoamine neurotransmitters in the brain. Together, our findings provide further insight into the pathways regulating monoamine neurotransmitter disposition in the brain.

Until recently, it was thought that MAO and SSAO were the only monoamine oxidases expressed in humans. The discovery of a novel FAD-dependent protein, renalase, was reported in 2005.[7] Renalase was identified using an *in silico* approach that aimed to discover novel proteins secreted by the kidney. The renalase protein sequence contains a highly conserved N-terminal FAD-binding domain and an amine oxidoreductase domain. Renalase shares low sequence identity with MAO-A and MAO-B (17 and 20 %, respectively) but, nonetheless, its predicted secondary and tertiary structures closely resemble those of MAO-B.[8] Recombinant renalase was shown to generate hydrogen peroxide in the presence of monoamines (including catecholamines), suggesting that it may share the catecholamine-degrading activity of MAO-A and B.[7] This activity was greatest in the presence of dopamine (followed by adrenaline and noradrenaline),[7] but it was not inhibited by MAO inhibitors, indicating differences in the possible catecholamine-degrading actions of these proteins.