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Flight behaviour in humans is intensified by a candidate genetic risk factor for panic disorder: evidence from a translational model of fear and anxiety

Panic Disorder (PD) is a serious and common psychiatric condition[1] characterised chiefly by recurrent episodes of intense, uncontrollable fear known as panic attacks.[2] The underlying causal mechanism for PD is unknown[3], however the discovery that drugs with clinical effectiveness against PD preferentially alter rodent flight behaviour suggests that PD reflects alterations in the brain systems that govern flight.[4] An association between PD and flight in humans is supported anecdotally by the tendency for PD sufferers to feel a strong urge to flee from the location where a panic attack occurs.[2] Here we provide the first human empirical evidence for a PD-flight link, showing that flight behaviour is significantly more intense in carriers of a candidate genetic risk factor for PD than in non-carriers.

Human flight behaviour was measured with a computerised translation of a rodent runway task (figure 1 a) designed to index fear-proneness behaviourally, as the intensity of flight effort in response to a pursuing threat stimulus.[5] The genetic risk factor for PD used in this study was the C allele of the 102T/C single nucleotide polymorphism (rs6313) within the serotonin 2a receptor gene (*HTR2A*) on chromosome 13q14.2; the C allele in this SNP is known to be associated with increased susceptibility to pure but not co-morbid panic disorder (PD)[6] as well as increased intensity of panic symptoms.[7] All 200 participants (107 males) gave informed consent and self-identified as healthy Caucasians. Buccal cells were collected and DNA extracted using established methods, see Supplementary Information.

The genotype distribution of rs6313 SNP in *HTR2A* was in Hardy–Weinberg equilibrium ($\chi 2 = 0.632$ df = 2, $p = 0.73$). There were no significant genotype effects

upon flight intensity (F (1,192) = 2.69, P = 0.070); however, carriers of the C risk allele displayed significantly greater flight intensity than TT individuals (F (1,194) = 4.90, P = 0.033; Figure 1b). The construct validity of flight intensity as a specific measure of fear-proneness was supported by its significant positive association with scores on tissue damage fear (measured by the Fear Survey Schedule) (F (1,194) = 5.92, P = 0.022) and its lack of a significant association with scores on Spielberger trait anxiety (F (1,194) = 0.01, P = 0.998), a widely accepted questionnaire measure of anxiety-proneness.[8] Sex did not affect flight intensity in this model (F (1, 194) = 1.50, P = 0.222) nor was there a significant allele x sex interaction (F (1, 194) = 1.56, P = 0.213). There was no significant interaction between tissue damage fear and rs6313 carrier status (C carrier or TT homozygote) (F (1,191) = 0.44, P = 0.511).

In overview, therefore, our study is the first molecular genetic investigation of human defensive behaviour and the first study empirically to support in humans the hypothesis that panic disorder stems from alterations in the brain systems governing flight behaviour. However, although the *HTR2A* gene on chromosome 13q4-21 has previously been associated with PD, as a caveat it should be noted that the rs6313 SNP in exon 1 of the coding sequence of the *HTR2A* gene is a synonymous (or silent) polymorphism. Therefore, its previously observed effects at the phenotypic level may be mediated not by changes in protein structure but via gene expression resulting, e.g., in changes in serotonin receptor density. As rs6313 is part of a 4-SNP haplotype (rs6311, rs1328674, rs6313, rs6314), future attempts at understanding the causative mechanisms underlying the association between the C allele in rs6313 and flight intensity should ultimately consider these other linked polymorphisms.[9,10]

While our findings suggest that PD is mediated by the brain systems that govern flight behaviour, our molecular genetic design could not reveal which brain

systems may be implicated. In rats electrical stimulation of the dorsal periaqueductal grey (PAG) prompts flight behaviour suggesting that this structure may be particularly relevant to determining susceptibility to PD. Therefore a desirable next step would be functional neuroimaging studies using our runway task that explore brain activity during flight. Additionally it would be desirable from an individual perspective to explore whether or not individuals that flee intensely and report being especially prone to fear show particularly intense activity in the target brain systems.

Finally, a strength of the use of healthy participants in this study is that the heightened flight reactions of C allele carriers cannot easily be explained as an outcome of acute symptomatic effects of PD or a side effect of medication for PD but instead may be part of an inherited trait of fearfulness/flight-proneness[3] that could ultimately constitute an endophenotype[11] for PD. However, this view should be tempered with the consideration that individuals without the C allele (i.e., who had the TT genotype) are relatively rare (only 18 males and 12 female in the present sample). The minority status of the TT individuals, therefore, implies that molecular genetic studies of the present type should invert the interpretation of their results, portraying TT carriers as unusually resistant to fear/PD rather than the carriers of the C allele as particularly prone to fear/PD.

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Supplementary Information is available at the Molecular Psychiatry website (http://www.nature.com/mp)

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Figure legend

Figure 1 (a) The Joystick Operated Runway Task, a computerised human translation of the Mouse Defense Test Battery. The participants used a force-sensing joystick apparatus (PH-JS1, Psyal, London, UK) to control the speed of a cursor (green dot) pursued along an on-screen runway by a threat stimulus (red dot). In order to provide aversive motivation for flight, if the red dot caught the green dot participants received an unpleasant but harmless 115dB white noise burst lasting 250ms. In order to mimic the calorie cost of flight in real threat situations, the velocity of the green dot increased in proportion to the force applied to the joystick. In order to control for individual differences in strength and motivation, the minimum force required for the green dot cursor to reach escape velocity was set at 50% of whatever maximum force that the participant exerted during an earlier calibration session. (b) Flight intensity was significantly increased by carrying the C allele of the 102T/C polymorphism (rs6313) within the serotonin 2a receptor gene (*HTR2A*; error bars represent 1 SEM; *$P < 0.05$.).