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# SHORT COMMUNICATION
# Variations in the human cannabinoid receptor (*CNR1*) gene modulate striatal responses to happy faces

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## Abstract

Happy facial expressions are innate social rewards and evoke a response in the striatum, a region known for its role in reward processing in rats, primates and humans. The cannabinoid receptor 1 (CNR1) is the best-characterized molecule of the endocannabinoid system, involved in processing rewards. We hypothesized that genetic variation in human *CNR1* gene would predict differences in the striatal response to happy faces. In a 3T functional magnetic resonance imaging (fMRI) scanning study on 19 Caucasian volunteers, we report that four single nucleotide polymorphisms (SNPs) in the *CNR1* locus modulate differential striatal response to happy but not to disgust faces. This suggests a role for the variations of the *CNR1* gene in underlying social reward responsivity. Future studies should aim to replicate this finding with a balanced design in a larger sample, but these preliminary results suggest neural responsivity to emotional and socially rewarding stimuli varies as a function of *CNR1* genotype. This has implications for medical conditions involving hypo-responsivity to emotional and social stimuli, such as autism.

## Introduction

An increasing body of research shows that both the experience and recognition of basic emotions might be subserved by common brain structures. For example, e.g. disgust is processed in the anterior insula and fear is processed in the amygdala (Calder *et al*., 2001). In a separate line of research, primate and rat studies have demonstrated that the striatum and the substantia nigra play a specific role in reward processing (Kawagoe *et al*., 1998; Schultz *et al*., 2000; Parkinson *et al*., 2000). These regions are also associated with reward processing in humans [receiving food rewards (O'Doherty *et al*., 2002), viewing funny cartoons (Mobbs *et al*., 2003), remembering happy events (Damasio *et al*., 2000)] and viewing happy faces (Phillips *et al*., 1998; Lawrence, *et al*., 2004). For a meta-review, see Phan *et al*. (2002). These two lines of research can be combined, in that viewing happy facial expressions functions as a social reward. There is considerable evidence for the rewarding role a happy face plays in humans from infancy onwards(Argyle, 1972; Trevarthen, 1974; Tronick *et al*., 1978).

The endocannabinoid system is one of the neuropeptidergic circuits involved in reward processing. This works in tandem with the mesolimbic dopaminergic system. The cannabinoid receptor 1 (CNR1) is the best-studied molecule of this system. It inhibits GABAergic neurons presynaptically in the hippocampus (Hoffman *et al*., 2003) and in the amygdala (Katona *et al*., 2001). Retrograde endocannabinoid signalling mediated through the CNR1 has been suggested as a possible mechanism for extinction of aversive memories (Azad *et al*., 2004; Cannich *et al*., 2004). Immunolocalization studies in rats and humans indicate high CNR1 expression levels in the striatum (Gardner & Vorel, 1998; Freund *et al*., 2003; Hurley *et al*., 2003; Fusco *et al*., 2004). CNR1 is involved in inhibiting the amplitude of miniature inhibitory postsynaptic currents (IPSCs) in GABA-ergic medium spiny neurons in the striatum (Szabo *et al*., 1998). More recently, CNR1 has been suggested to modulate striatal dopamine release through a *trans*-synaptic mechanism, involving both GABA-ergic and glutamatergic synapses (van der Stelt & Di Marzo, 2003). Phasic release of striatal dopamine plays a central role in reward processing (Schultz, 2002). In the study reported here, we test if CNR1 also plays a role in social reward processing, specifically in modulating activity in brain regions activated by viewing happy faces.

Previous studies have employed a similar hypothesis-driven approach to correlate genotype with an 'intermediate phenotype' [neural response to a particular class of stimuli, as measured by functional magnetic resonance imaging (fMRI)]. These include the effect of a brain derived neurotrophic factor (*BDNF*) polymorphism on hippocampal response to a verbal episodic memory task (Egan *et al*., 2003), the effect of a catechol-*o*-methyl transferase (*COMT*) polymorphism on prefrontal cortical response in a working memory task (Egan *et al*., 2001) and the effect of a serotonin transporter (*SERT*) promoter polymorphism on amygdala response to an emotion response (using fear faces) task (Hariri *et al*., 2002).

In the light of these previous studies, we hypothesized that *CNR1* polymorphisms would underlie individual differences in striatal response to a social reward like happy faces. This is different from the previous studies in that we study multiple single nucleotide polymorphisms (SNPs) from the same gene. We chose four different

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multiply validated SNPs within the CNR1 locus (see Fig. 1B). Recent studies of a single polymorphism (of unknown functionality) on the *TPH2* gene have been shown to influence amygdala reactivity to emotional stimuli. Using a similar approach, we chose the four SNPs with a high minor allele frequency [possibly playing a broader role in brain function and susceptibility to psychopathological conditions (Brown *et al*., 2005)], and spanning the whole gene (no two SNPs being more than seven kilobases apart).

rs1049353 is a synonymous C/T SNP, located in coding exon 4, which may have functional consequences such as effects on mRNA translation, secondary structure (Shen *et al*., 1999) and consequently stability (Duan *et al*., 2003; Capon *et al*., 2004). rs806377 is located in untranslated exon 3, which is possibly involved in regulating gene expression (Zhang *et al*., 2004). SNPs rs6454674 and rs806380 are intronic, but have been found to exist in strong linkage disequilibrium with the two other SNPs in a larger population. [Linkage disequilibrium

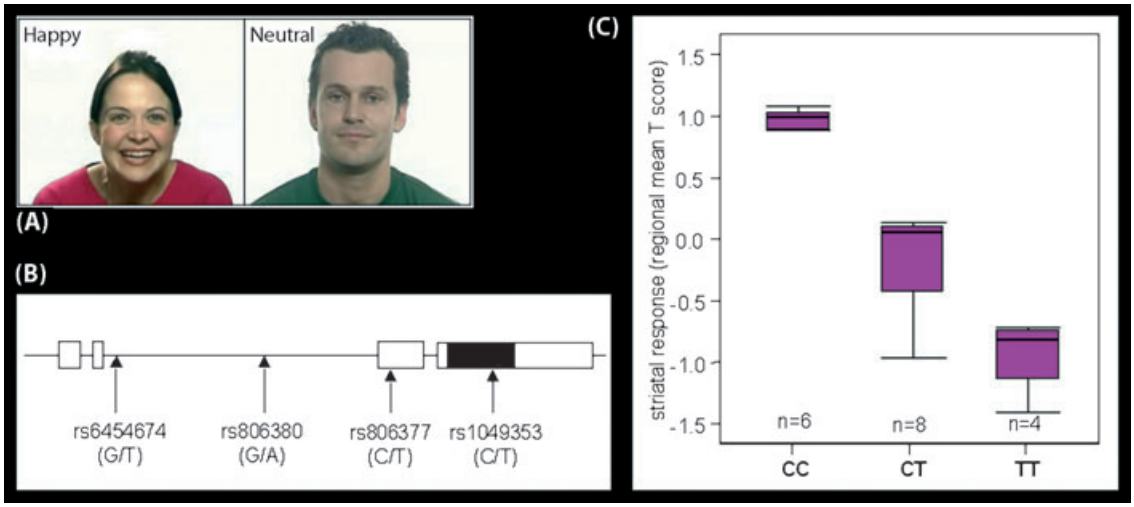


FIG. 1. (A) Example stills from stimuli clips showing happy and neutral expressions. (B) Schematic representation of the *CNR1* gene indicating the relative locations of the four genotyped SNPs [adapted from Zhang *et al*. (2004)]. The black box indicates a coding exon, white boxes indicate untranslated exons, and the intervening line indicates intronic sequence. (C) The striatal response (regional mean *t* score) to the [happy–neutral] contrast, grouped by individual genotypes (CC, CT, TT) of the SNP rs806377 (single outlier has been excluded for illustration purposes only) (significant at $P < 0.01$). In panel C the red bars indicate SEMs, and the horizontal lines are means and SDs. The significant group differences (all at $P < 0.01$) in striatal cluster response for the other three SNPs were as follows: rs1049353, CT > CC; rs806380, GG > AA and GG > AG: rs6454674, GG > GT and GG > TT.

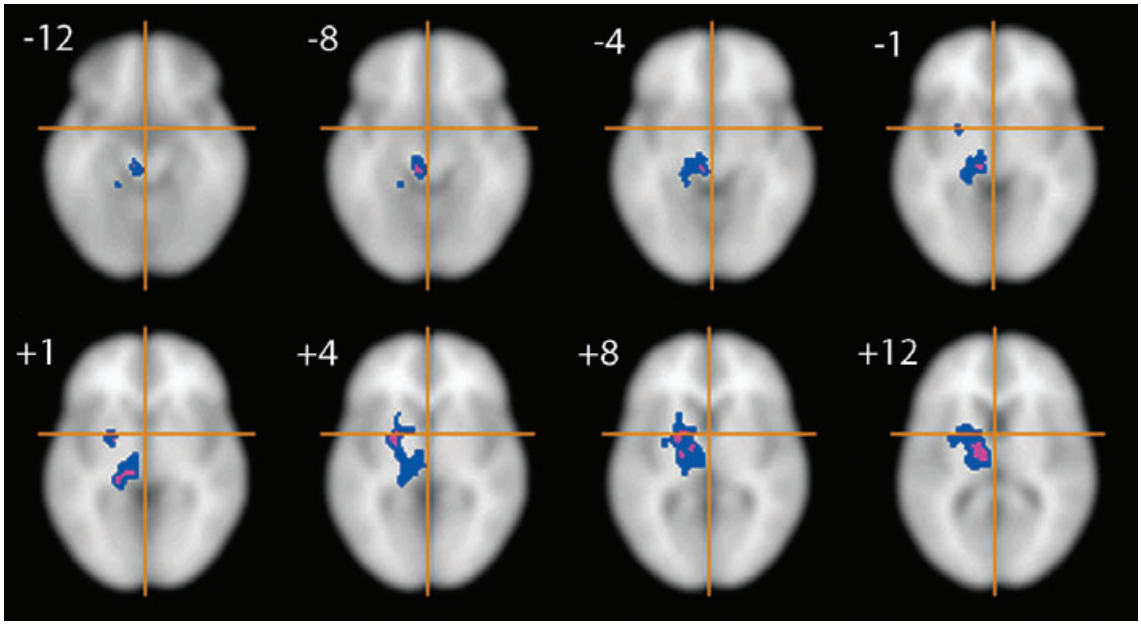


FIG. 2. Generic brain activation maps showing genotype group differences (significant at $P < 0.01$, clusterwise probability) in striatal response to [happy–neutral] contrast, for the polymorphism rs806377, superimposed in standard Talairach space (Talairach & Tournoux, 1988). The colour change from blue to purple indicates regions where the magnitude changes by more than 25% of the maximum value.

(*D*) was calculated using SNPSpD (Nyholt, 2004) for a large Caucasian population genotyped for these SNPs ($n = 359$, from which the volunteers for the scanning experiment were selected at random). genotyped for these SNPs. Significant *D*-values were observed between the different SNPs. (For rs806377 vs. rs806380, $D = 1.00$; for rs806377 vs. rs6454674, $D = 1.00$; rs806380 vs. rs6454674 $D = 0.914$; all at $P < 0.000001$. For rs1049353 vs. rs806380, $D = 0.556$; for rs1049353 vs. rs6454674, $D = 0.5$, all at $P < 0.0003$.)].

The experimental condition was the perception of happy facial expressions. In designing the control condition, we chose an emotion that was reliably linked with a striatal response. The only other emotion that has been consistently shown to evoke a response in the basal ganglia region is disgust (Phan *et al*., 2002). There is little consistency in the existing literature (Murphy *et al*., 2003) on a striatal response to any other basic emotion. Hence, to ensure that any observed effect was not just due to CNR1 being expressed in that region, and was specific to the perception of happy faces, we used facial expressions of disgust as control stimuli. Our hypothesis was that genotypic variations of some or all of these SNPs would predict differences in the magnitude of striatal response to happy faces, but not to disgust faces, relative to neutral faces.

## Materials and methods

Nineteen Caucasian student participants (ten males, nine females) matched for age, IQ and educational background with no history of head injury/operation or regular drug abuse, were recruited by advertisement. All participants had given informed written consent as approved by the Cambridge Local Research Ethics Committee. DNA was genotyped using standard ABI assays (http://www.appliedbiosystems.com). Following this, 21 near-axial/oblique-axial slices (4-mm thick) of gradient-echo echo-planar imaging (EPI) data depicting blood oxygen level dependent (BOLD) contrast were acquired using a 3T MRI scanner (Bruker, Ettlingen) with the following parameters: in-plane resolution 2.2 mm × 2.2 mm; repetition time 1093 ms; echo time 30 ms; flip angle 65.5°. Four blocks each of happy, disgust and neutral facial expressions (Fig. 1A) of different actors (each block containing four 3-s video clips, 1-s ISI) and a low-level baseline (a fixation cross) were visually presented in a pseudo-random order in a box-car design. Participants were instructed to press a button for every stimulus seen.

## Analysis and Results

The functional imaging data was preprocessed using SPM2, using the Automatic Analysis pipeline (http://www.mrc-cbu.cam.ac.uk/~rhodri/aa/). General linear modelling (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/spm2/) was used to estimate the contrast statistics [happy–neutral] and [disgust–neutral[ at each voxel for individual participant. Random effects analysis across all participants revealed activation clusters in the fusiform gyrus to (neutral faces vs. the low level baseline), the left inferior frontal gyrus/anterior insula to (disgust faces vs. neutral faces) and the posterior cingulate cortex and putamen to (happy faces vs. neutral faces) (Chakrabarti *et al*., 2005). These activations replicate several earlier findings (Phan *et al*., 2002), which provides some validation for the stimuli used.

To determine the effect of genotype for each SNP on the striatal response to happy faces, we performed four analyses of variance with the [happy–neutral] contrast images as the dependent variable and the individual genotypes as the independent (grouping) variable (Fig. 1B and C) in each analysis. Non-parametric permutation tests have been shown to be more efficient in dealing with small sample sizes when compared to parametric tests (Nichols & Hayasaka, 2003). Hence, a randomization-based permutation test (XBAMM, http://www-bmu.psychiatry.cam.ac.uk/software/docs/xbamm/index1.html) was used. This revealed significant effects of all four SNPs at a whole brain level (all maps thresholded with clusterwise $P < 0.01$ by permutation test; equivalent to less than one false positive error per map, using the procedure as described in Bullmore *et al*. (1999).

Significant regions for each SNP included the putamen-pallidal region. *Posthoc t*-tests revealed significant differences in this striatal cluster response between genotypes for each SNP (see Fig. 2) for map of activation differences associated with a single, indicative SNP, rs806377, see Table 1 for voxel coordinates of the striatal regions showing differential response for each (SNP). An exactly equivalent analysis with the [disgust–neutral] contrast images revealed no effect of any SNP.

TABLE 1. Talairach coordinates of striatal regions showing differential activation as a main effect of genotype, grouped by individual polymorphisms

| | Talairach coordinates (mm) | | |
|---|---|---|---|
| Polymorphisms and regions | *x* | *y* | *z* |
| rs1049353 | | | |
| Putamen/globus pallidus | −35.1 | −6.0 | 1.0 |
| Putamen/globus pallidus | −31.7 | −3.5 | 4.0 |
| Caudate nucleus | −29.7 | −31.7 | 8.0 |
| Putamen | −27.3 | −21.5 | 12.0 |
| Caudate nucleus | −36.7 | −35.3 | 12.0 |
| Putamen | −37.9 | 0.6 | 16.0 |
| Caudate nucleus | −30.4 | −20.3 | 16.0 |
| Caudate nucleus | −37.8 | −35.5 | 16.0 |
| rs806377 | | | |
| Brain stem | −3.3 | −25.3 | −4.0 |
| Putamen/globus pallidus | 25.2 | −0.2 | −1.0 |
| Putamen/globus pallidus | 24.2 | −2.1 | 1.0 |
| Putamen | 17.1 | −11.9 | 4.0 |
| Thalamus | 17.2 | −8.2 | 8.0 |
| Putamen | 18.2 | −7.7 | 12.0 |
| Putamen | 27.0 | 0.3 | 16.0 |
| rs806380 | | | |
| Brain stem | 5.0 | −19.0 | −12.0 |
| Brain stem | −10.6 | −11.5 | −8.0 |
| Brain stem | 4.8 | −18.4 | −8.0 |
| Brain stem | −7.1 | −9.4 | −4.0 |
| Brain stem | −0.4 | −5.8 | −1.0 |
| Putamen/globus pallidus | −17.2 | −10.8 | −1.0 |
| Thalamus | −0.3 | −6.0 | 1.0 |
| Putamen/globus pallidus | −20.0 | −8.0 | 1.0 |
| Thalamus | 0.9 | −19.0 | 4.0 |
| Thalamus | 3.0 | −18.5 | 8.0 |
| Thalamus | 7.7 | −16.3 | 12.0 |
| rs6454674 | | | |
| Brain stem | 4.2 | −5.1 | −8.0 |
| Brain stem | 0.5 | −26.0 | −4.0 |
| Caudate nucleus | 3.2 | 3.1 | −1.0 |
| Brain stem | 3.1 | −21.9 | −1.0 |
| Caudate nucleus | 2.7 | 5.9 | 1.0 |
| Thalamus | 3.0 | −11.0 | 1.0 |
| Caudate nucleus | 4.6 | 11.2 | 4.0 |
| Caudate nucleus | −10.7 | 6.7 | 4.0 |
| Thalamus | 23.0 | −30.8 | 4.0 |
| Caudate nucleus | 8.6 | 11.3 | 8.0 |
| Caudate nucleus | 18.1 | −27.9 | 8.0 |
| Caudate nucleus | 14.4 | 7.2 | 12.0 |
| Caudate nucleus | 13.7 | −25.2 | 12.0 |
| Caudate nucleus | 12.2 | −24.7 | 16.0 |

To ensure that the observed effects were specific to happy and not to disgust faces, we estimated the contrast [happy–disgust] for each voxel for each subject. We then performed analyses of variance (as described above) with the [happy–disgust] contrast values as the dependent variable and the genotypes for each SNP as the independent variable. This revealed significant effects at a whole brain level ($P < 0.01$) in the same striatal region for the SNPs rs1049353, rs806380 and rs6454674.

## Discussion

The experiment reported here tested if striatal response measured using fMRI in human volunteers viewing happy faces varied as a function of genotypic differences at the *CNR1* locus. The results show that four SNPs spanning the *CNR1* gene (rs1049353, rs806377, rs806380, rs6454674) modulated the striatal response to happy faces and not to disgust faces. These effects might be mediated through subtle alterations of the binding affinities of the CNR1 protein to its endogenous ligands (2-arachidonylglycerol and anandamide) in these regions. It is known that the CNR1 exhibits very high binding affinities to its endogenous ligands in this region, and hence possibly even small variations could underlie significant changes in binding affinities. We make these mechanistic speculations in the light of previous findings that have found that synonymous SNPs from coding sequences (Duan *et al*., 2003; Capon *et al*., 2004) can affect expression and/or activity of the translated protein through altering mRNA structure and stability. This, taken together with the role of CNR1 in the phasic release of dopamine in the striatum (the best known neural signature of reward) suggests that the observed effects reflect subtle individual differences in reward processing.

While the effects of the different alleles on the expression and/or activity profiles of the CNR1 protein are not well known, our findings represent a potential lead where an observed systems-level effect provides potential candidates for elucidation of underlying molecular mechanisms (Brown *et al*., 2005). It is possible that one or more of these SNPs are 'functional' at a cellular level, and the observed effects are due to the other SNPs being in linkage disequilibrium with it or them. This must be considered as being an exploratory study because of the relatively small sample size ($n = 19$) and unequal number of participants in each genotype group. It will therefore be important to attempt to replicate these findings in future studies with larger samples and fully balanced designs. In order to ensure that the observed results are specific to the perception of happy and not disgust faces, we performed two separate analyses that yielded concordant results.

The role of CNR1 in addiction vulnerability (a special case of reward responsivity) in humans has been suggested (Zhang *et al*., 2004). To our knowledge, this is the first study to show that DNA sequence variants of proteins expressed within the physiological substrate of the reward system in the brain reflect differential neural responses to social rewards such as happy faces. As happy (but not disgust) faces are innately socially rewarding, the results from this study are consistent with predictions from this literature and suggest a possible role for CNR1 genetic variations in individual differences in social reward responsivity. As viewing happy faces is also a specific case of emotion processing, the results may also have implications for neurodevelopmental conditions with a genetic basis in which social-emotional responsivity is under-active or atypical in function, such as autism (Hobson, 1986; Baron-Cohen, Ring *et al*., 1999; C. Ashwin, …, unbublished results).

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## Abbreviations

CNR1, cannabinoid receptor 1; fMRI, functional magnetic resonance imaging; SNP, single nucleotide polymorphism.

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