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Risk-taking in humans and the medial orbitofrontal cortex reward system

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ABSTRACT

Risk-taking differs between humans, and is associated with the personality measures of impulsivity and sensation-seeking. To analyse the brain systems involved, self-report risk-taking, resting state functional connectivity, and related behavioral measures were analyzed in 18,740 participants of both sexes from the UK Biobank. Functional connectivities of the medial orbitofrontal cortex, ventromedial prefrontal cortex (VMPFC), and the parahippocampal areas were significantly higher in the risk-taking group ($p < 0.001$, FDR corrected). The risk-taking measure was validated in that it was significantly associated with alcohol drinking amount ($r = 0.08$, $p = 5.1\times10^{-28}$), cannabis use ($r = 0.12$, $p = 6.0\times10^{-66}$), and anxious feelings ($r = -0.12$, $p = 7.6\times^{-98}$). The functional connectivity findings were cross-validated in two independent datasets. The higher functional connectivity of the medial orbitofrontal cortex and VMPFC included higher connectivity with the anterior cingulate cortex, which provides a route for these reward-related regions to have a greater influence on action in risk-taking individuals. In conclusion, the medial orbitofrontal cortex, which is involved in reward value and pleasure, was found to be related to risk-taking, which is associated with impulsivity. An implication is that risk-taking is driven by specific orbitofrontal cortex reward systems, and is different for different rewards which are represented differently in the brains of different individuals. This is an advance in understanding the bases and mechanisms of risk-taking in humans, given that the orbitofrontal cortex, VMPFC and anterior cingulate cortex are highly developed in humans, and that risk-taking can be reported in humans.

1. Introduction

Risk-taking can influence all of us, and differs between different people. Here we show that risk-taking is related to how strongly the medial orbitofrontal cortex is connected with other brain systems. The medial orbitofrontal cortex is involved in reward, and represents different rewards differently in different people. This provides a neurobiological basis for risk-taking to be different in different people, and moreover to be different for different types of goal or reward. The findings provide new insights into risk-taking behavior that have potential applications in many aspects of life in humans.

Risk-taking is the tendency to take risks when people make decisions or aim for goals, and is associated with impulsivity and sensation-seeking (Green and Myerson, 2013). A fractionation of impulsive behavior has been proposed that includes: 'waiting impulsivity' (measured for example by delay discounting), 'stopping impulsivity' (measured by the stop-signal task), and 'risky impulsivity' (Dalley and Robbins, 2017). Further facets of impulsivity that include sensation-seeking, negative urgency, positive urgency, premeditation, and perseverance have been proposed (Stamates and Lau-Barraco, 2017a). The fractionation suggests that impulsivity has several subtypes, and that these subtypes may depend on distinct neural systems. Indeed, it is suggested (Rolls, 2019c, 2021) that risky impulsivity might arise because of high sensitivity or connectivity of the human medial orbitofrontal cortex which is involved in reward, or low sensitivity or connectivity of the lateral orbitofrontal cortex which is involved in punishment/non-reward (Grabenhorst and Rolls, 2011; Rolls, 2019c, d; Rolls et al., 2020; Rolls, 2021). Risk-taking is associated with drug use, alcohol use, gambling problems, and risky sexual behavior (Bjork and Pardini, 2015; Braams et al., 2016; Stamates and Lau-Barraco, 2017b; Chuang et al., 2017; Lydon-Staley et al., 2020). Previous neural studies have shown that higher ventral striatum activation to rewards is correlated with risk-taking behavior in the form of more alcohol use (Braams et al., 2016); and that risk-seeking attitudes are associated with increased activation of the orbitofrontal cortex in a gambling task (Blankenstein et al., 2017). Further, sensation-seeking, which is often associated with risky impulsivity (MacPherson et al., 2010; Ruedl et al., 2012), is positively correlated

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with the functional connectivity between the medial orbitofrontal cortex and anterior cingulate cortex in the Nathan-Kline-Institute dataset (Wan et al., 2020). Increased functional connectivities involving the medial orbitofrontal cortex in alcohol drinkers are also correlated with impulsiveness (Cheng et al., 2019). These findings support the hypothesis that one type of risky impulsivity is led by reward sensitivity, and is associated with substance use. Further, different reward types are represented by different neurons in the orbitofrontal cortex (Rolls, 2014, 2016b, 2019c, d; Rolls et al., 2020), and the reward sensitivity of the orbitofrontal cortex in different individuals is different for different types of reward (for example in chocolate cravers (Rolls and McCabe, 2007)), and this could have implications for understanding risk-taking, as described here.

The aim of the present study is to investigate how brain functional connectivity is related to risk-taking using a very large neuroimaging sample of 18,740 participants from the UK Biobank. Functional connectivity is measured by the correlation between the fMRI BOLD signal between each pair of brain areas, with a high functional connectivity providing an indication of strong interactions and mechanistic effects between brain areas that may influence function. A feature of the investigation is that risk-taking was measured by self-report from the human participants, whereas performance in tasks thought to be related to risky behavior needs to be used in animal studies. The measure of risky behavior used here was shown to be valid, in that other measures such as whether the individual is a worrier were (negatively) correlated with it, and alcohol and drug use were positively correlated with the report measure of risky behavior. The hypotheses investigated were whether the reward-related medial orbitofrontal cortex has high functional connectivity in risk-takers; whether the punishment/non-reward lateral orbitofrontal cortex has low functional connectivity in risk-takers; whether some other neural systems have their functional connectivity significantly related to self-reported human risk-taking; and whether the report measure of risk-taking is related to substance use and other behavioral measures such as worrier status.

2. Methods

2.1. UK Biobank dataset

The UK Biobank is a large-scale biomedical database and research resource dedicated to improving the prevention, diagnosis, and treatment of various diseases (Miller et al., 2016) (https://biobank.ctsu.ox.ac.uk). It follows the health status, medical history, and well-being of 500,000 volunteers aged between 37 and 73 years and provides health information to approved researchers from academia and industry. These participants underwent cognitive performance, mental health and physical assessments, provided detailed information of their backgrounds, living environment, and general behavioural pattern, and agreed to have their health followed longitudinally. 19,528 participants with resting-state fMRI data available after quality control are the main cohort investigated in this study, with 10,323 females and 9,205 males (aged from 45 to 79, mean 61.8), and 18,740 participants also had the measure of risk-taking.

2.2. Behavior measures

The risk-taking measure used (UK Biobank data field ID 2040) was the response to the question: "Would you describe yourself as someone who takes risks?". An answer of 'Yes' was scored 1, and of 'No' 0. Participants who reported 'Do not know' or 'Prefer not to answer' were excluded, leaving 29,956 participants with risk-taking data from release 1 of the UK Biobank.

A worrier/anxious feelings measure (UK Biobank data field ID 1980) also used was the response to the question: "Are you a worrier?". Scoring was as for the risk-taking measure, and provided 30,237 participants, 15,134 of whom provided a response of 'Yes'.

2.3. Resting state fMRI neuroimaging and pre-processing

The multi-modal imaging was collected using a standard Siemens Skyra 3T running VD13A SP4, with a standard Siemens 32-channel RF receive head coil. The resting-state functional brain imaging data used in this study included 18,740 participants. The details of the image acquisition are provided at the UK Biobank website in the form of a protocol (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367). All the quality checking and data preprocessing procedures were conducted by the UK Biobank and the details of the preprocessing are available on the UK Biobank website (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977) and elsewhere (Miller et al., 2016). Briefly, data pre-processing was carried out using FSL (FMRIB Software Library). All the data preprocessing procedures were performed by the UK Biobank team as described in (Miller et al., 2016). The data preprocessing included correction for spatial and gradient distortions and head motion, intensity normalization and bias field removal, registration to the T1 weighted structural image, transformation to 2 mm Montreal Neurological Institute (MNI) space, and the FIX artefact removal procedure (Smith et al., 2013; Navarro Schroder et al., 2015). Finally, the head motion parameters were regressed out and structured artefacts were removed by ICA+FIX processing (Independent Component Analysis followed by FMRIB's ICA-based X-noiseifier (Salimi-Khorshidi et al., 2014; Griffanti et al., 2014)). The data preprocessing pipeline developed by FMRIB (Oxford University Centre for Functional MRI of the Brain) used here has been widely used in resting state fMRI studies (Smith et al., 2015; Navarro Schroder et al., 2015; Colclough et al., 2017; Vidaurre et al., 2018).

2.4. t-tests on functional connectivity differences between risk-taking and non-risk-taking groups

Functional connectivity was computed by performing a Pearson correlation of the BOLD signal averaged across the whole resting-state neuroimaging time between each pair of brain areas (Biswal et al., 1995). In this study, the brain regions were used and defined by the automated anatomical labelling atlas AAL2 (Rolls et al., 2015). This AAL2 atlas includes 94 brain regions spanning the whole cerebrum, excluding the cerebellum, with the areas listed in Table S2. It was used because it has a good parcellation of the orbitofrontal cortex (Rolls et al., 2015). The time series of each pair of brain areas were extracted first. Then, the Pearson correlation between these two time courses was calculated to measure functional connectivity for each participant. To improve the normality of the correlation coefficients, the Fisher's r-to-z transformation was performed, which results in a 94 by 94 symmetric matrix in which each value represents one link between every pair of brain regions.

Two-sample two-tailed t-tests were used to test whether risk-taking is associated with functional connectivity, using FDR correction (Benjamini and Hochberg, 1995) for multiple comparisons. The confounding effects of age, sex, education, head motion (mean framewise displacements), and site information were removed in this analysis. 18,740 participants who had available both resting-state fMRI and risk-taking data were included in the t-test, including 4,891 risk-taking people and 13,849 non-risk-taking people. We note that correlation was used for continuous variables, and t tests for categorical variables.

2.5. Cross-validation datasets and analyses

2.5.1. UK Biobank release 2

One cross-validation performed was with release 2 of the UK Biobank dataset for which 5,699 independent participants had the necessary neuroimaging and risk-taking data. The data were processed in the same way as for release 1. Then a Spearman correlation was performed to assess the association between whole-brain functional connectivity and the risk-taking score across all participants, separately for release 1 and

Table 1
Behavior level association between risk-taking, worrier/anxious feelings, drug use, and alcohol use.

	Drinking Amount		Heavy Drink Frequency		Cannabis Use	
Risk-taking	*r* value	*p* value	*r value*	*p value*	*r value*	*p value*
	0.078	5.14E-28	0.098	1.18E-41	0.117	5.99E-66
Worrier	*r value*	*p value*	*r value*	*p value*	*r value*	*p value*
	-0.039	5.15E-08	-0.053	4.96E-14	-0.026	1.53E-04

release 2. In more detail, a partial correlation was performed between functional connectivities and the risk-taking score with 5 confounding variables regressed out: age, gender, education, site information and head motion (mean framewise displacement). To validate the results, the correlation (r) values for every link in the correlation matrix with the risk-taking score were compared.

2.5.2. NKI dataset

With the same brain atlas, partial correlation between the risk-taking and the functional connectivities with all participants with available fMRI and risk-taking measures from the Nathan-Kline Institute (NKI) dataset ($N = 411$) was performed with age, gender and head motion regressed out (Nooner et al., 2012). The processing of the NKI data was as described elsewhere (Wan et al., 2020). Then the correlation between the correlation matrix of risk-taking with FCs in the UK Biobank dataset and the correlation matrix of risk-taking with FCs in the NKI dataset was calculated. The risk-taking score was provided by the Domain-Specific Risk-Taking Scale (DOSPERT) (Blais and Weber, 2006), which assesses risk-taking in five content domains: financial decisions (separately for investing versus gambling), health/safety, recreational, ethical, and social decisions. The overall risk-taking score was used in this investigation.

3. Results

3.1. Functional connectivity differences between the risk-taking and non-risk-taking groups

778 (of the 4371) functional connectivities were significantly different between the risk-taking and non-risk-taking groups ($p < 0.001$, FDR corrected) based on the analysis with 18,740 participants in the UK Biobank release 1. The numbers of different functional connectivity links for different brain regions are shown in Fig. 1. The full matrix of the t values of functional connectivities different between the risk-taking and non-risk-taking groups is shown in Fig. 2. The brain regions with significantly different higher functional connectivities included the medial orbitofrontal cortex areas (OFCmed, rectus, OFCpost), and ventromedial prefrontal cortex (VMPFC) (Frontal Med Orb in Fig. 2), with regions that included the cingulate cortex, temporal cortical areas, visual cortical areas including the fusiform and some parietal cortex areas (Fig. 2). The parahippocampal gyrus showed higher functional connectivity with many of the same temporal lobe and other visual cortical areas in the risk-taking group (Fig. 2). Some other sensory/motor areas had higher functional connectivity in the risk-taking group, including the postcentral gyrus (somatosensory) together with the Rolandic operculum and precentral cortex; and Heschl's gyrus (auditory) (Fig. 2). The lateral orbitofrontal cortex areas (OFClat and the laterally adjacent FrontalInfOrb2) showed relatively few significant differences in functional connectivity between the risk-taking and non-risk-taking groups (Figs. 1 and 2).

3.2. Worrier/anxious feelings, drug use and alcohol use are associated with risk-taking behavior

Those who reported taking risks also tended to report that they were not worriers: the worrier/anxious feeling measure was negatively correlated with the risk-taking measure with $r = -0.122$ ($p = 7.62\times10^{-98}$) at the behavioral level ($N = 29{,}275$). Because whether an individual is a worrier might involve to some extent similar brain systems involved in risk-taking (in that worriers might be less likely to take risks), the functional connectivities in the worrier group ($N = 9576$) vs the non-worrier group ($N = 9322$) were measured, with the t values shown in Fig. 3A. 712 functional connectivities were significantly different between the worrier/anxious feelings and the non-worrier/anxious feelings groups ($p < 0.01$, FDR corrected) (Fig. 3A). Links involving the VMPFC (FrontalMedOrb) and adjacent medial orbitofrontal cortex (rectus) were lower in the worrier group; as were links involving the parahippocampal gyrus/ hippocampus, the cingulate cortex, and some temporal lobe areas.

Comparison of Figs. 2 and 3A indicates that some of the functional connectivity links that are higher in risk-takers are lower in worriers. To check the overall relationship, for every link, the t value for the difference related to worrier status is compared with the t value related to risk in Fig. 3B. In general, brain regions with a high value for risk have a low value for worrier status, and across all AAL2 brain areas the inverse relationship is strong and significant ($r = -0.66$, $p < 10^{-20}$). Thus brain areas with high functional connectivity related to risk-taking tend to have low functional connectivity related to worrier status.

The risk-taking measure used here was also associated with other behaviors. Table 1 shows that risk-taking was associated with cannabis use ($r = 0.12$, $p = 8.8\times10^{-65)}$, with the frequency of consuming large amounts of alcohol ($r = 0.10$, $p = 1.2\times10^{-41}$), and with the amount of alcohol drunk ($r = 0.078$, $p = 5.1\times10^{-28}$) (Table 1). This shows that the risk-taking self-report measure used here has validity in that it is associated with behaviors that are associated with risk-taking measured in other ways as set out in the literature described in the second paragraph of the Introduction, including worrier status, cannabis use, and alcohol consumption.

Consistent with the negative correlation between worrier feelings and risking and the involved functional connectivities, worrier status was negatively correlated with cannabis use, with the frequency of consuming large amounts alcohol, and with the amount of alcohol drunk, as shown in Table 1.

Because the risk-taking self-report measure was correlated with alcohol and drug use, and worrier status, the functional connectivities associated with risk-taking were further analysed with these factors regressed out as covariates of no interest. The results were that the differences in functional connectivity shown in Fig. 2 remained significant at $p < 0.005$ FDR corrected. Indeed, the correlation between the functional connectivities shown in Fig. 2 and the functional connectivities with alcohol use, cannabis use, and worrier status regressed out was 0.92 ($p < 10^{-323}$). Thus the correlation between risk-taking and functional connectivities shown in Fig. 2 remains strong and highly significant when covariates such as drug use and anxiety are regressed out.

3.3. Cross-validation with independent data groups of the relation between functional connectivity and risk-taking

Validations with the risk-taking and impulsiveness in other datasets were performed to test whether the findings on functional connectivity are consistent. The cross-validation involved tests of whether the findings in the UK Biobank dataset Release 1 about risk-taking could be replicated or find support from other datasets. (It was confirmed that the correlation measures utilised were not significant with mea-

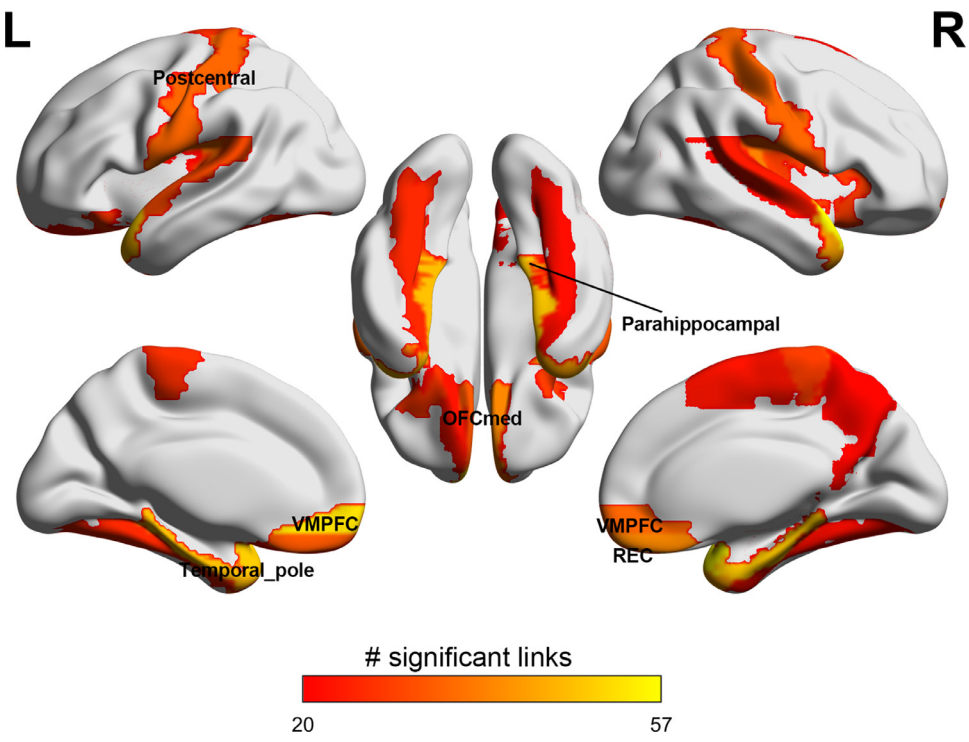

Fig 1. Brain areas with many functional connectivity links that were higher in the risk-taking than non-risk-taking group included the medial orbitofrontal cortex (OFCmed and REC (rectus)) and ventromedial prefrontal cortex (VMPFC). The numbers of functional connectivity links that were significantly higher ($p < 0.001$, FDR corrected) in a brain area in the risk-taking group are shown. The lateral surface of the human brain is shown above, the medial surface below, and the ventral surface in the middle.

sures from the UK Biobank that are unlikely to be related to risk-taking. These included total food weight consumed on the previous day (field ID 100001) for which $r = -0.00043$ $p = 0.98$; and body mass index (field ID 21001) for which $r = -0.024$ $p = 0.11$.)

3.3.1. NKI dataset

The 94×94 correlation matrix of the functional connectivities with the risk-taking score from 411 participants in the NKI dataset was compared with the corresponding correlation matrix from the UK Biobank data. As shown in Fig. 4A in which each point is for a different brain region in the aal2 atlas, brain regions with high correlations with risk-taking in the UK Biobank dataset tended to have high correlations with risk-taking also in the NKI dataset, and vice versa. The overall correlation across all brain regions was 0.12 ($p = 3.3\times10^{-15}$). Thus brain regions with high correlations with risk-taking in the UK Biobank dataset tended highly significantly to also have high correlations in the NKI dataset, providing cross-validation in the form of support from an independent dataset.

3.3.2. UK Biobank release 2

The same procedure was followed for the second release of UK Biobank data, with 5,699 participants with risk-taking scores and fMRI data available in the second release. The correlation between the correlation matrix between functional connectivities and risk-taking with FCs in the UK Biobank dataset release 1 and the correlation matrix between functional connectivities and risk-taking with FCs in the Biobank dataset release 2 was 0.67 ($p < 10^{-20}$) shown in Fig. 4B, providing cross-validation in the form of support from independent participants.

4. Discussion

A key finding is that the functional connectivities of the human medial orbitofrontal cortex and ventromedial prefrontal cortex (VMPFC) are positively correlated with self-reported risk-taking behavior. The finding is highly robust, in that it was obtained from neuroimaging in 18,740 participants in the UK Biobank dataset, with $p < 0.001$ FDR corrected for multiple comparisons (Figs. 1 and 2), involved correlations in the order of 0.06 for individual brain regions, and was cross-validated in two independent datasets. Part of the interest of this is that the human medial orbitofrontal cortex is implicated in reward value representations (Rolls, 2019c, d; Rolls et al., 2020), including for olfactory, flavor, touch and visual rewards (Kringelbach and Rolls, 2003; Kringelbach et al., 2003; de Araujo et al., 2003; Grabenhorst et al., 2008; Grabenhorst and Rolls, 2008), even extending to include monetary reward (O'Doherty et al., 2001; Xie et al., 2021), face expressions (Kringelbach and Rolls, 2003), face beauty (O'Doherty et al., 2003), and amphetamine (Völlm et al., 2004). In humans the medial orbitofrontal cortex is not only activated by many rewarding stimuli but also reflects their subjective pleasantness (Grabenhorst and Rolls, 2011; Rolls, 2019c). This is found for odors (Rolls et al., 2003a), flavor (Kringelbach et al., 2003; de Araujo et al., 2003), and pleasant touch. Humans with orbitofrontal cortex lesions may also be less sensitive to reward, as shown by their reduced subjective emotional feelings and altered social and emotional behavior and problems with face expression processing (Rolls et al., 1994; Hornak et al., 1996; Hornak et al., 2003). Given this background, an implication of the present findings is that a factor that drives risk-taking in humans is how strongly connected the medial orbitofrontal cortex reward system is with other brain regions. The concept that is implied is that it is differences in the reward system in different individuals that is an important driving factor in human risk-taking, which is one type of impulsivity. Given that there is a genetic component to risk-taking in humans (Kreek et al., 2005; Cesarini et al., 2009; Heitland et al., 2012; Strawbridge et al., 2018; Karlsson Linner et al., 2019), it is possible that one way in which evolution shapes human behavior is by setting the sensitivity of different reward systems each separately represented in the orbitofrontal cortex as shown by neuronal recordings (Rolls, 2019c, d, 2021) to be different in different humans (Rolls, 2014). An interesting implication of these concepts is that risk-taking in humans is different for different types of reward, which is largely unexplored.

An alternative concept and hypothesis that was tested is that risk-taking is influenced by low sensitivity to non-reward and punishment of

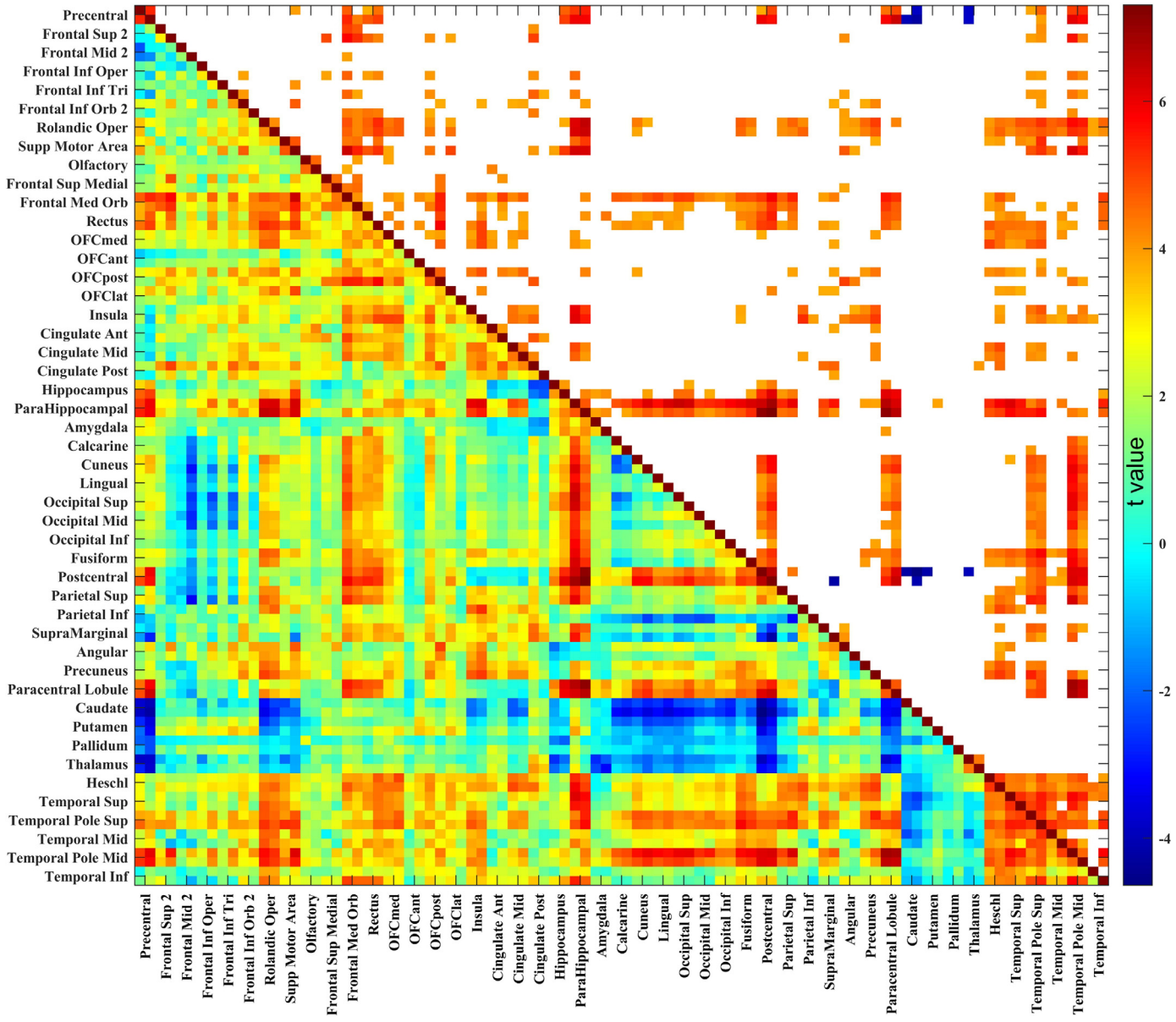

Fig 2. Higher functional connectivitites were found in the risk-taking group in the medial orbitofrontal cortex and some sensory areas. The differences in functional connectivity in the risk-taking group compared to the non-risk-taking group. The matrix of t values is shown, with positive values showing links that were higher in the risk-taking group. The lower triangle matrix shows the functional connectivity across all links of the risk-taking group relative to the non-risk-taking group. The upper triangle matrix shows significant links with $p < 0.001$ FDR corrected. The number of participants was 18,740 from the UK Biobank release 1. The AAL2 brain areas are listed in Table 2.

the lateral orbitofrontal cortex (Rolls, 2019c, d; Rolls et al., 2020), but this was not reflected in any clear functional connectivity differences of the lateral orbitofrontal cortex in risk-takers in the present investigation (Fig. 2).

One area with which the medial orbitofrontal cortex / VMPFC has high functional connectivity in risk-takers is the cingulate cortex (Fig. 2). There are major connections from the medial orbitofrontal cortex / VMPFC reward areas to especially the pregenual anterior cingulate cortex (Hsu et al., 2020; Du et al., 2020; Rolls et al., 2022) which is also activated by rewards (Grabenhorst and Rolls, 2011) and which may be part of a cingulate cortex system to enable actions to be guided by the rewards that are available (Rushworth et al., 2007; Rolls, 2019a). Sensation-seeking, another aspect of impulsivity, is related in a similar way to the strength of the connectivity between the medial orbitofrontal cortex and the anterior cingulate cortex (Wan et al., 2020). A mechanistic interpretation is that the higher functional connectivity between the medial orbitofrontal cortex/VMPFC and the anterior cingulate cortex in risk-takers reflects stronger influences between these brain regions, which could result in a greater influence of reward on action, given that the medial orbitofrontal to anterior cingulate system is implicated in reward influences on actions (Rushworth et al., 2007; Rolls, 2019a). Part of the interest of this finding is that even in the resting state, the functional connectivity between these brain areas is higher in risk-takers, which supports the hypothesis of underlying differences in the brains of different individuals that relate to risk-taking.

The medial orbitofrontal cortex / VMPFC also has high functional connectivity with temporal lobe and related visual cortical areas (Fig. 2), and this may reflect strong coupling of visual sensory inputs to the reward system in risk-taking humans. The same strong driving by sensory inputs may apply to the strong connectivity of other sensory areas (e.g.

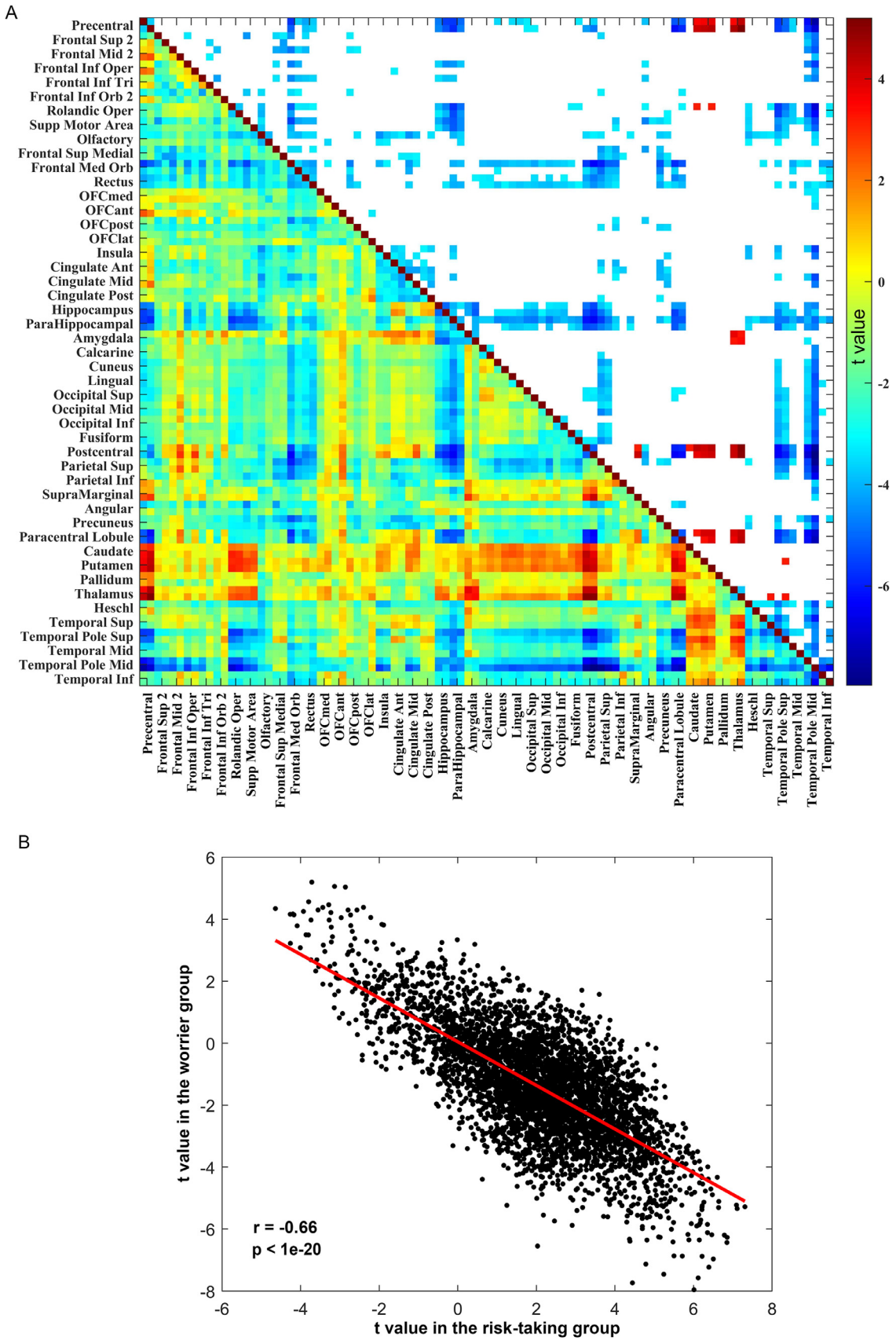

Fig. 3. (A) The difference in functional connectivity in the worrier/anxious feelings group. The matrix of t values for the worrier/anxious feelings group. The lower triangle matrix shows the functional connectivity across all links of the worrier/anxious feelings group relative to the non- worrier/anxious feelings group. The upper triangle matrix shows significant links with $p < 0.01$ FDR corrected. The data are from 18,898 UK Biobank participants. (Fig 2B_a.tif).
(B) Scatter plots and fitting curves between the t values (differences of functional connectivity) in the risk-taking group and the worrier/anxious feelings group. Each data point is for a functional connectivity link in the AAL2 atlas.

Table 2
The anatomical regions defined in each hemisphere and their label in the automated anatomical labelling atlas AAL2 (Rolls et al., 2015). Column 4 provides a set of possible abbreviations for the anatomical descriptions.

NO.	ANATOMICAL DESCRIPTION	LABEL aal2.nii.gz	POSSIBLE ABBREVIATION
1,2	Precentral gyrus	Precentral	PreCG
3, 4	Superior frontal gyrus, dorsolateral	Frontal_Sup	SFG
5, 6	Middle frontal gyrus	Frontal_Mid	MFG
7, 8	Inferior frontal gyrus, opercular part	Frontal_Inf_Oper	IFGoperc
9, 10	Inferior frontal gyrus, triangular part	Frontal_Inf_Tri	IFGtriang
11, 12	IFG pars orbitalis,	Frontal_Inf_Orb	IFGorb
13, 14	Rolandic operculum	Rolandic_Oper	ROL
15, 16	Supplementary motor area	Supp_Motor_Area	SMA
17, 18	Olfactory cortex	Olfactory	OLF
19, 20	Superior frontal gyrus, medial	Frontal_Sup_Med	SFGmedial
21, 22	Superior frontal gyrus, medial orbital	Frontal_Med_Orb	PFCventmed
23, 24	Gyrus rectus	Rectus	REC
25, 26	Medial orbital gyrus	OFCmed	OFCmed
27, 28	Anterior orbital gyrus	OFCant	OFCant
29, 30	Posterior orbital gyrus	OFCpost	OFCpost
31, 32	Lateral orbital gyrus	OFClat	OFClat
33, 34	Insula	Insula	INS
35, 36	Anterior cingulate & paracingulate gyri	Cingulate_Ant	ACC
37, 38	Middle cingulate & paracingulate gyri	Cingulate_Mid	MCC
39, 40	Posterior cingulate gyrus	Cingulate_Post	PCC
41, 42	Hippocampus	Hippocampus	HIP
43, 44	Parahippocampal gyrus	ParaHippocampal	PHG
45, 46	Amygdala	Amygdala	AMYG
47, 48	Calcarine fissure and surrounding cortex	Calcarine	CAL
49, 50	Cuneus	Cuneus	CUN
51, 52	Lingual gyrus	Lingual	LING
53, 54	Superior occipital gyrus	Occipital_Sup	SOG
55, 56	Middle occipital gyrus	Occipital_Mid	MOG
57, 58	Inferior occipital gyrus	Occipital_Inf	IOG
59, 60	Fusiform gyrus	Fusiform	FFG
61, 62	Postcentral gyrus	Postcentral	PoCG
63, 64	Superior parietal gyrus	Parietal_Sup	SPG
65, 66	Inferior parietal gyrus, excluding supramarginal and angular gyri	Parietal_Inf	IPG
67, 68	SupraMarginal gyrus	SupraMarginal	SMG
69, 70	Angular gyrus	Angular	ANG
71, 72	Precuneus	Precuneus	PCUN
73, 74	Paracentral lobule	Paracentral_Lobule	PCL
75, 76	Caudate nucleus	Caudate	CAU
77, 78	Lenticular nucleus, Putamen	Putamen	PUT
79, 80	Lenticular nucleus, Pallidum	Pallidum	PAL
81, 82	Thalamus	Thalamus	THA
83, 84	Heschl's gyrus	Heschl	HES
85, 86	Superior temporal gyrus	Temporal_Sup	STG
87, 88	Temporal pole: superior temporal gyrus	Temporal_Pole_Sup	TPOsup
89, 90	Middle temporal gyrus	Temporal_Mid	MTG
91, 92	Temporal pole: middle temporal gyrus	Temporal_Pole_Mid	TPOmid
93, 94	Inferior temporal gyrus	Temporal_Inf	ITG

Heschl's gyrus for auditory, and post-central and related areas for somatosensory inputs) with the medial orbitofrontal cortex / VMPFC reward areas (Fig. 2) (Hsu et al., 2020; Du et al., 2020; Rolls et al., 2022). The higher functional connectivity of the parahippocampal gyrus with many brain areas (including visual temporal and related areas, and to some extent the orbitofrontal cortex and VMPFC), is more difficult to relate to risk-taking, but may relate to especially active memory systems (Rolls, 2018a, 2021) in risk-takers, which is also largely unexplored.

The worrier/anxious feelings measure was correlated with risk-taking with r = -0.12 ($p < 10^{-20}$) at the behavioral level. In relation to the brain, some of the FC links involving the medial orbitofrontal cortex / VMPFC areas were positively correlated with risk-taking (Fig. 2) and negatively correlated with worrier/anxious feelings (Fig. 3A). It is a possibility suggested by the similarity of the connectivities that worrier / anxiety status is low at least partly because the reward system dominates the worry.

Drug use and alcohol use were positively correlated with the risk-taking measure described here (Table 1). A possible implication is that drug and alcohol use are associated with the high connectivity of the medial orbitofrontal cortex reward system, which at the same time leads to what may be risk-taking in order to obtain high rewards, consistent with an earlier study (Cheng et al., 2019). However, the finding that risk-taking is associated with high functional connectivity of the medial orbitofrontal cortex and VMPFC was shown to not be due just to the fact that risk-taking is associated with drug use and worrier status, for the higher functional connectivities of the medial orbitofrontal cortex and VMPFC were still highly significant in risk-takers (at $p < 0.005$ FDR) when drug use and worrier status were regressed out as covariates of no interest.

The human self-report measure of risk-taking used here is of considerable interest, for it enabled extension of understanding of the brain systems related to risk-taking to something that can be reported by humans. A primary finding presented here is that self-reported risk-taking is associated with higher functional connectivity of brain systems including the medial orbitofrontal cortex that are involved in reward. But we did go on to show that the measure of risk-taking was valid by the findings of correlations with drug use and anxiety. The evidence about the brain systems related to this measure of risk-taking in humans is important, for the brain systems found to be related to the risk-taking including the orbitofrontal cortex, VMPFC, and anterior cingulate cortex

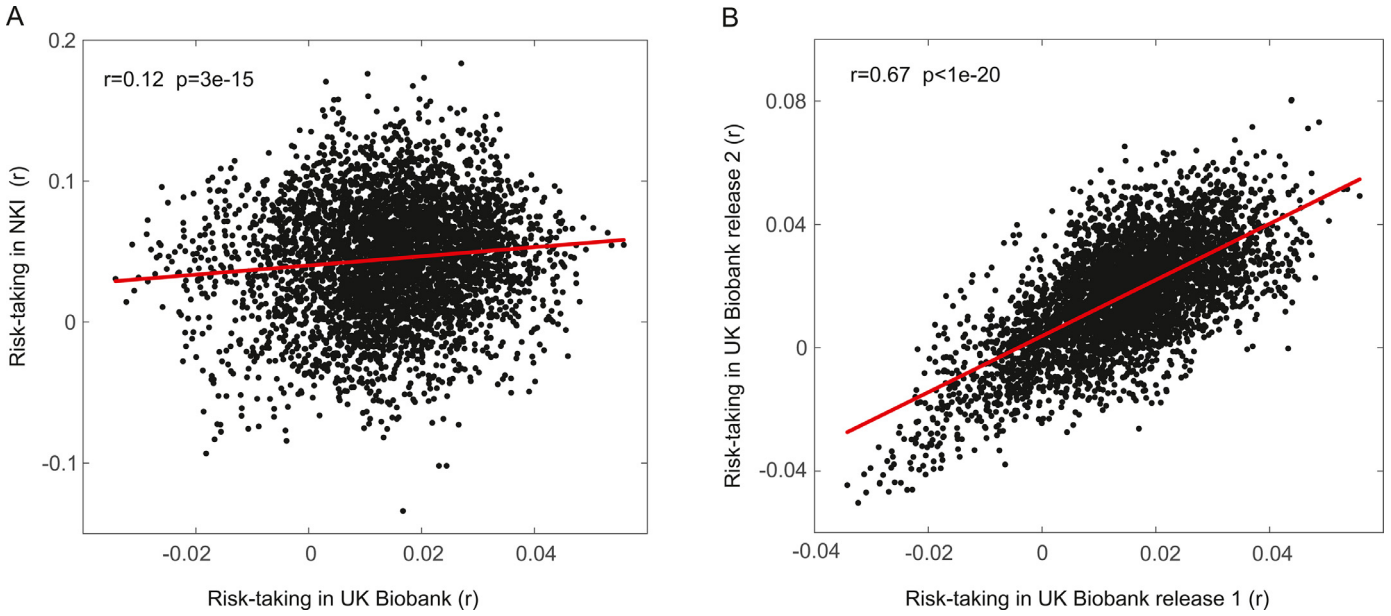

Fig 4. Cross-validations of functional connectivities (FC) related to risk-taking with data from other independent datasets. A) The correlation between the correlation matrix of risk-taking with FCs in the UK Biobank dataset and the correlation matrix of risk-taking with FCs in the NKI dataset was 0.12 ($p = 3.3\times10^{-15}$). Each point is for an AAL2 functional connectivity link, and shows the correlation between the FC of one link with risk-taking in the UK Biobank dataset (horizontal axis) and with risk-taking in the NKI dataset (vertical axis). B) The correlation between the correlation matrix of risk-taking with FCs in the UK Biobank dataset and the correlation matrix of the risk-taking with FCs in the second release of data in the UK Biobank was 0.67 ($p < 10^{-20}$). Each point is for an AAL2 functional connectivity link, and shows the correlation between the FC of one link with risk-taking in UK Biobank release 1 (horizontal axis, 18740 participants) and UK Biobank release 2 (vertical axis, 5,699 participants).

have developed very greatly in primates including humans compared to rodents (Vogt, 2009; Passingham and Wise, 2012; Rolls, 2019b, c, 2021). It will be of interest in future research to analyse what possible fractionates of risk-taking (Stamates and Lau-Barraco, 2017a; Dalley and Robbins, 2017) may be especially related to the risk-taking brain systems described here in humans.

Possible limitations are considered next. Small vessel disease may influence resting state fMRI, and is likely to be associated with age (Hussein et al., 2020; Schulz et al., 2021). The influence of this was minimized by regressing out age in all of the analyses. In addition, when a measure of vascular health, blood pressure, was regressed out as a covariate of no interest, the correlation of the t-value matrices for the correlations between functional connectivities and risk taking without (Fig. 2) and with this covariate included was $r = 0.9995$, suggesting that the risk-taking finding was not related to at least blood pressure differences. It has also been suggested in a population of 289 participants that a risk propensity measure is higher in males than females with possible functional connectivity differences associated with this (Zhou et al., 2014), but in the present investigation with a very much larger sample (18,740 participants in UK Biobank Release 1), significant differences between males and females in the functional connectivities described here related to self-reported risk taking were not found.

In conclusion, the medial orbitofrontal cortex / VMPFC, which is implicated in reward processing, has functional connectivity that is high in risk-takers. An implication is that some types of risk-taking may be related to high efficacy including connectivity of the reward valuation system in humans. An interesting implication for understanding risk-taking better in humans is that risk-taking may be different for different types of reward, for different rewards are separately represented in the orbitofrontal cortex. This is thus an extension of the concept of different reward systems for different types of reward in the orbitofrontal cortex (based on neurophysiological evidence (Thorpe et al., 1983; Rolls et al., 1990; Rolls et al., 1996; Rolls et al., 1999; Rolls et al., 2003b; Kadohisa et al., 2004; Kadohisa et al., 2005; Rolls and Grabenhorst, 2008; Rolls, 2014; Rolls et al., 2018; Rolls, 2019c, d; Rolls et al., 2020)) providing a basis for understanding specificity in emotional (Rolls, 2014, 2018b) and motivational (Rolls, 2016a) systems, to also, it is now proposed, understanding the reward specificity of risk-taking. Given that risk-taking is a key aspect of human behavior that is of great importance throughout society, with different individuals showing different amounts of risk-taking, and it is now suggested different risk-taking for different types of reward, the findings and concepts described here have very important implications for society, and for safety whether in one's own behavior or in the behavior of others. The concepts developed here also lead to the proposal that risk-taking is more than a behavioral or personality trait, in that risk-taking may be different for different reward types, and may be understood in an overarching biological framework of specific reward systems in the brain (Rolls, 2014, Rolls, 2019c, 2021), which have implications not only for emotional and motivational behavior, but in addition for risk-taking. It is further proposed that risk-taking is also selective in terms of the punishers that are involved, with some individuals more sensitive to for example the lack of social reinforcement, and others to monetary loss. These concepts apply to risk-taking systems not only in humans, but also to risk-taking widely in the animal kingdom.

Declaration of Competing Interest

None.

Credit authorship contribution statement

Edmund T. Rolls: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Zhuo Wan:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Wei Cheng:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **Jianfeng Feng:** Funding

acquisition, Methodology, Project administration, Writing – review & editing.

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Data and code availability statement

The data analyzed are available from the UK Biobank (https://biobank.ctsu.ox.ac.uk). Standard code functions available in Matlab and SPM were used.

Ethics statement

No new data were collected in this investigation. The UK Biobank received ethical approval from the research ethics committee (REC reference 11/NW/0382). The present analyses were conducted under UK Biobank application number 1954. Written informed consent was obtained from each subject.

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