



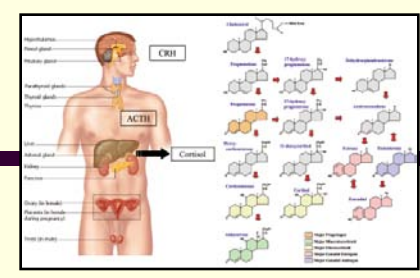
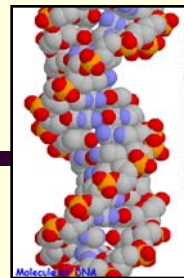
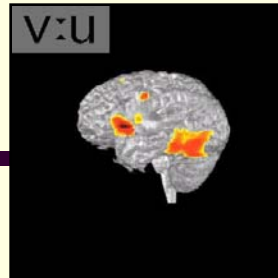
Understanding Human Response to Risk: An Overview of a Multidisciplinary Research Plan Involving Neuroscience, Genetics & Endocrinology

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Presentation Overview

- The grand research plan
 - The original idea and research design
- The implementation
 - What worked, what didn't and why
- What's going on now

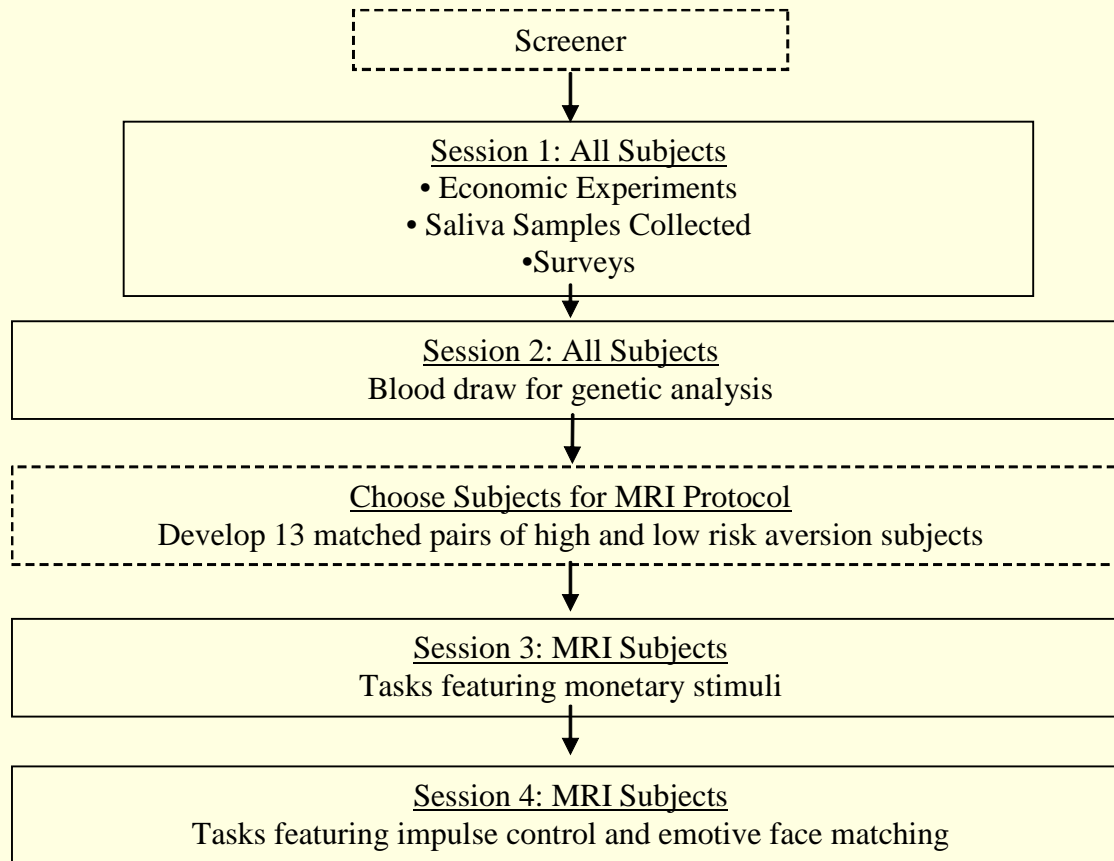
Key Question

- Why do people differ in their risk aversion (tolerance, attitudes interchangeably)?
 - The focus of the original research design
- Related questions
 - Is risk aversion constant through life?
 - What causes individual risk aversion to change?
 - Motivate interest in the original research design
 - Cannot be answered by data generated by the original design

Our Idea

- Combine existing protocol from
 - Experimental economics
 - Psychology
 - Neurology
 - Genetics
 - Endocrinology
- To isolate differences between subjects with high and low risk aversion

Our Protocol



Screener

- Measured
 - Economic risk aversion (hypothetical)
 - Psychological risk constructs
 - Prior to revelation that protocol required
 - fMRI, blood draw, sensitive surveys
- Screened for exclusion criteria
- Gauged willingness to participate in each element of protocol
 - fMRI, blood draw, sensitive surveys
- Scheduled interested recruits to available session times and dates

Session I – Behavior and Surveys

- Econ experiments of risk aversion
 - Modified Holt & Laury protocol (AER 2002)
- Psychometric constructs of risk attitudes
 - Novelty Seeking & Harm Avoidance
- Endocrine system measures
 - Salivary cortisol pre- & post-stressor
- Other surveys
 - Stressful Event History Calendar
 - Medical History
 - Gambling, Alcohol, Drug Use measures
 - Perception of severity of different types of risk
 - Demographic questionnaire

Session II - Genetics

- Went to campus med facility for blood draw
 - Done gratis by NIH funded center on campus
- DNA extracted
- Screen for genetic variations thought to affect
 - catecholamine function or
 - previously implicated in impulse control issues or associated with risk attitudes, including
 - Dopamine transporter & receptors
 - Serotonin transporter & receptor
 - Nicotine receptors
 - COMT (breaks down dopamine & other catecholamines)
 - VMAT (affects catecholamine transport) and others

Session III - Neuroimaging

- Identify a small # of high & low risk aversion types
- 3 tasks inside a fMRI scanner
 - Financial decision task (wheel of fortune task)
 - Striatum response scaled with risk faced
 - Impulse control task
 - Known to be deficient in pathological gamblers
 - Orbito-frontal activity known to scale with control
 - Emotive facial matching task
 - Known to recruit amygdala, which was previously implicated in responses to financial losses
- Key Question:
 - Would differences across the tails of our distribution of subjects show differential activation in these regions?

What Didn't Work

- Neuroimaging
 - Difficulty replicating literature results for the financial task
 - Image quality reduced by hardware problems
 - Co-PI and key graduate student handling this element left the university
- Lessons
 - Your neuro-collaborator(s) need to
 - operate in a university or other research environment that fully supports a good fMRI machine for research (not just a clinical MRI)

What has worked so far

■ Screener data

- Provided evidence that there is sample selection into experiments featuring MRI and blood sample based upon risk aversion
 - Roe et al. 2009 J. Econ. Psych.

■ Genetics

- Pilot data has revealed several associations with key polymorphisms that survive adjustments for multiple testing
 - Roe et al. (forthcoming). PLoS ONE

Genetics Paper

- Why are genetics results interesting?
 - Genes are switches, not blueprints
 - Environmental factors can switch them on/off
 - Intergenerational transmission of behavioral tendencies may be of interest
 - Genetic differences can be a source of heterogeneity in preferences not yet documented

Past genetic work on risk attitudes

- Limited economic work
 - Twin studies of heritability of risk attitudes
 - ~ 20% for paying gambles experiment by Cesnari et al. ('09 *QJE*) among Swedish twins
 - ~ 60% for paying gambles experiment by Zhong et al. ('09 *Twin Research*) among Chinese twins
 - Heritability only tells how likely is intergenerational transmission
 - Small sample association studies
 - Kuhnen & Chiao ('09 *PLoS ONE*) paying gamble choice with *DRD4* & *SERT* in 65 (males and females)
 - Dreber et al. ('09 *EvolHumBehav*) paying gambles and *DRD4* in 94 men
 - Roussos et al. ('08 *Neuropsychologia*) non-paying gambling task and *COMT* in 107 Greek males
 - Van der Bos et al. ('09 *Neuropharmacology*) non-paying gambling task and *SERT* & *COMT* in 70 females
- More work using psych risk attitudes – too numerous to mention

Our Study

- 67 subjects
 - 29 female, 8 non-white, age 20.6 ± 3.2
 - Excluded: left-handers, smokers
- 4 Measurements of Risk Attitude
 - 2 from economics literature
 - Large gambles - % safe option chosen
 - Gambles framed as gains - % safe option chosen
 - 2 from psych literature
 - Novelty seeking (NS), harm avoidance (HA)
- 98 polymorphisms (95 SNPs, 3 VNTRs)
 - Thought to affect catecholamine function (dopamine and others)
 - Or previously implicated w/ risk attitudes or impulse control
 - 14 were excluded because either
 - Not in Hardy-Weinberg equilibrium
 - Tests generational stability of the polymorphism
 - Had limited variation
 - <5% for less frequent variety
- Limited power due to sample size
 - 0.43 to find a large effect at 5% given a Bonferonni adjustment for 84 SNPs

Findings: Risk Attitudes

	Mean (s.e.)	Spearman Correlation Coeff. (p-values)			
		<u>NS</u>	<u>HA</u>	<u>SGL</u>	<u>SGG</u>
Novelty Seeking	0.44 (0.013)	1.00	--	--	--
Harm Avoidance	0.43 (0.018)	-0.41 (0.004)	1.00	--	--
% Safe Gambles Large	0.39 (0.02)	-0.06 (0.99)	0.01 (0.99)	1.00	--
% Safe Gambles Gains	0.40 (0.02)	-0.07 (0.99)	-0.18 (0.64)	0.89 (<0.001)	1.00

No significant correlation b/w econ and psych measures

Findings: Genetic Associations

- 2 SNPs affecting the nicotine receptor (*CHRNA4*) are significantly related to Harm Avoidance
 - rs4603829: $F=14.34$, $p = 0.029$
 - rs4522666: $F=11.95$, $p = 0.042$
 - p -values adjusted for multiple hypothesis testing via the False Discovery Rate method (FDR)
- The nicotine receptor is of interest because
 - it modulates the release of dopamine, serotonin & other neurotransmitters implicated in risk taking
 - *CHRNA4* is highly expressed in the central nervous system & important to mesolimbic dopamine function
 - rs4603829 has not been previously linked with a behavioral phenotype
 - rs4522666 previously associated with cigarette smoking behavior among schizophrenics
- Harm avoidance has been previously associated with pathological gambling

Findings: Additional Associations

- Also scanned for associations that were significant in the absence of adjustment for multiple testing
 - Stimulus for future work with larger samples
 - Found associations between
 - All econ and psych risk attitude measures and
 - Polymorphisms in
 - *COMT* and *MAOA* (both degrade catecholamines)
 - Dopamine transporter and receptors 2 & 3
 - Estrogen receptor
 - Norepinephrine transporter
 - tryptophan (affects serotonin synthesis)
 - *VMAT* (helps transport catecholamines in brain)

Summary: Genetics Paper

- More systematic research necessary to understand genetic underpinnings of risk attitudes
 - To make progress need a broader search across
 - Risk measures (econ, psych, etc)
 - Understand if different domains of risk behavior have unified or disparate genetic basis
 - Genes affecting reward processing