Advances in Understanding the Behavioral and Neurobiological Underpinnings of Motivational Deficits in Schizophrenia

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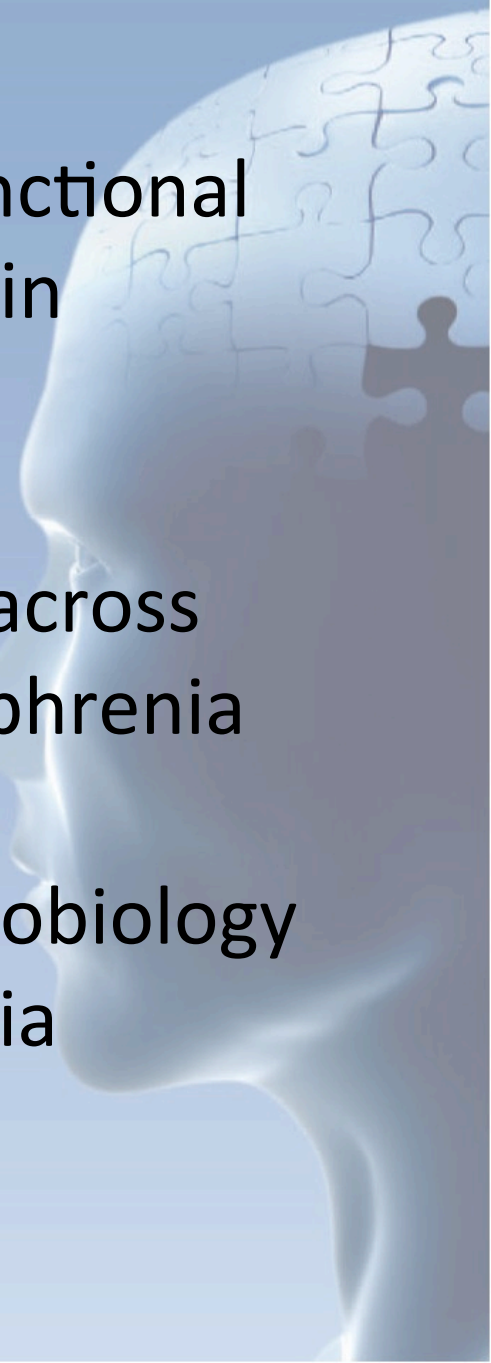
Disclosure slide

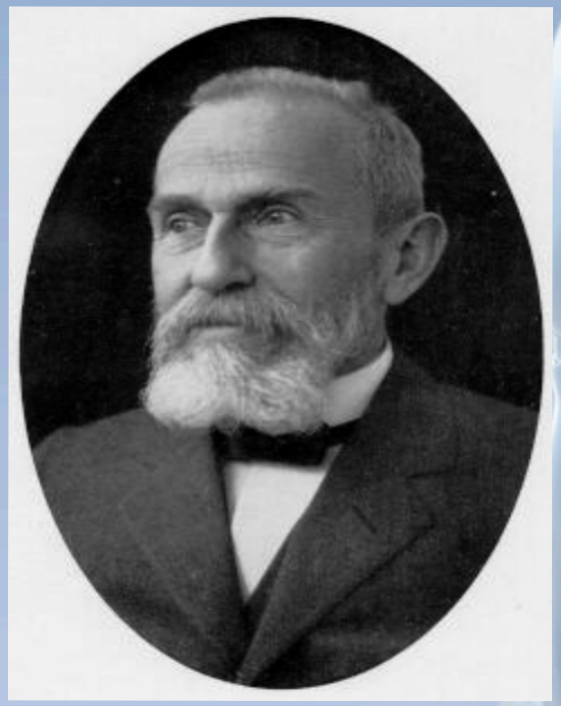
Conflict of interests	See below
Relevant relationships with companies	Companies
• Sponsoring or research money • Fee or other reimbursement (speaker's fees) • Shareholder • Other relationship – Advisory Board	• Neurocrine Bioscience, Medicure • Hoffman La-Roche, Novartis, Lundbeck • n/a • Hoffman La-Roche

Objectives

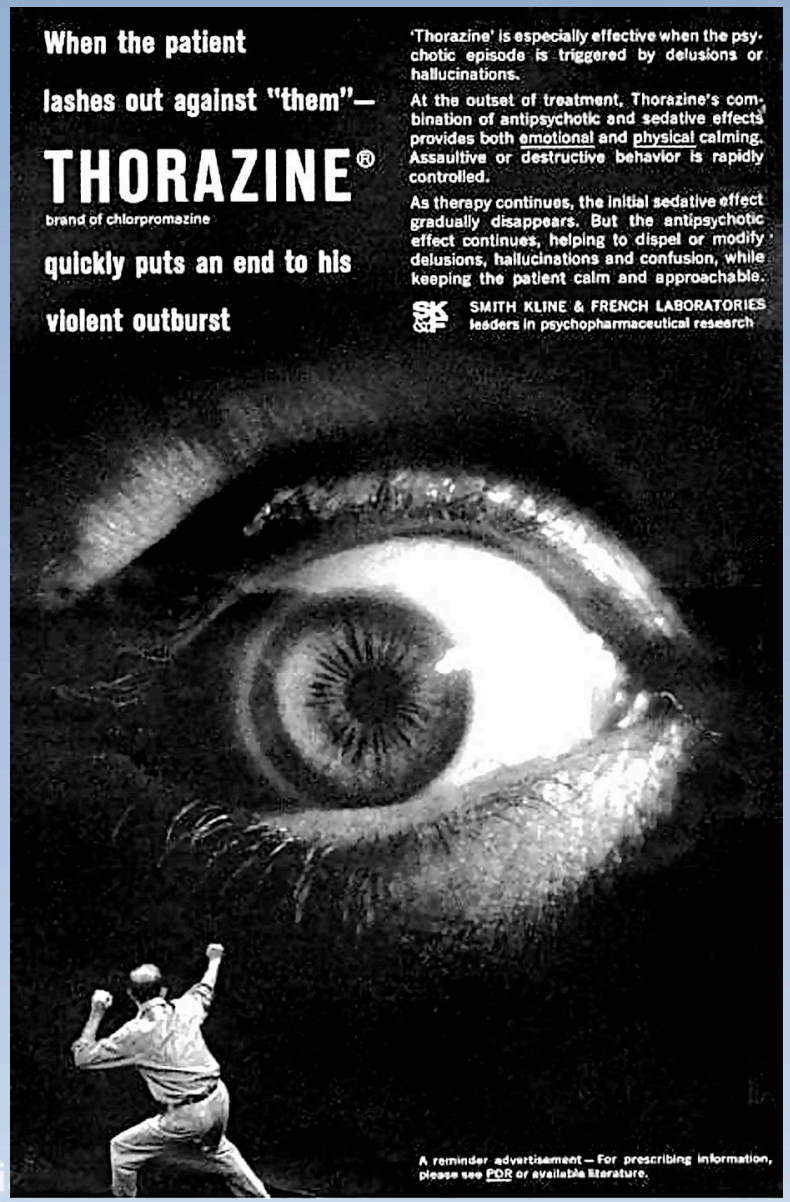
- To review the phenomenology and functional consequences of motivational deficits in schizophrenia
- To examine behavioural impairments across discrete facets of motivation in schizophrenia
- To explore recent findings on the neurobiology of cost/effort valuation in schizophrenia



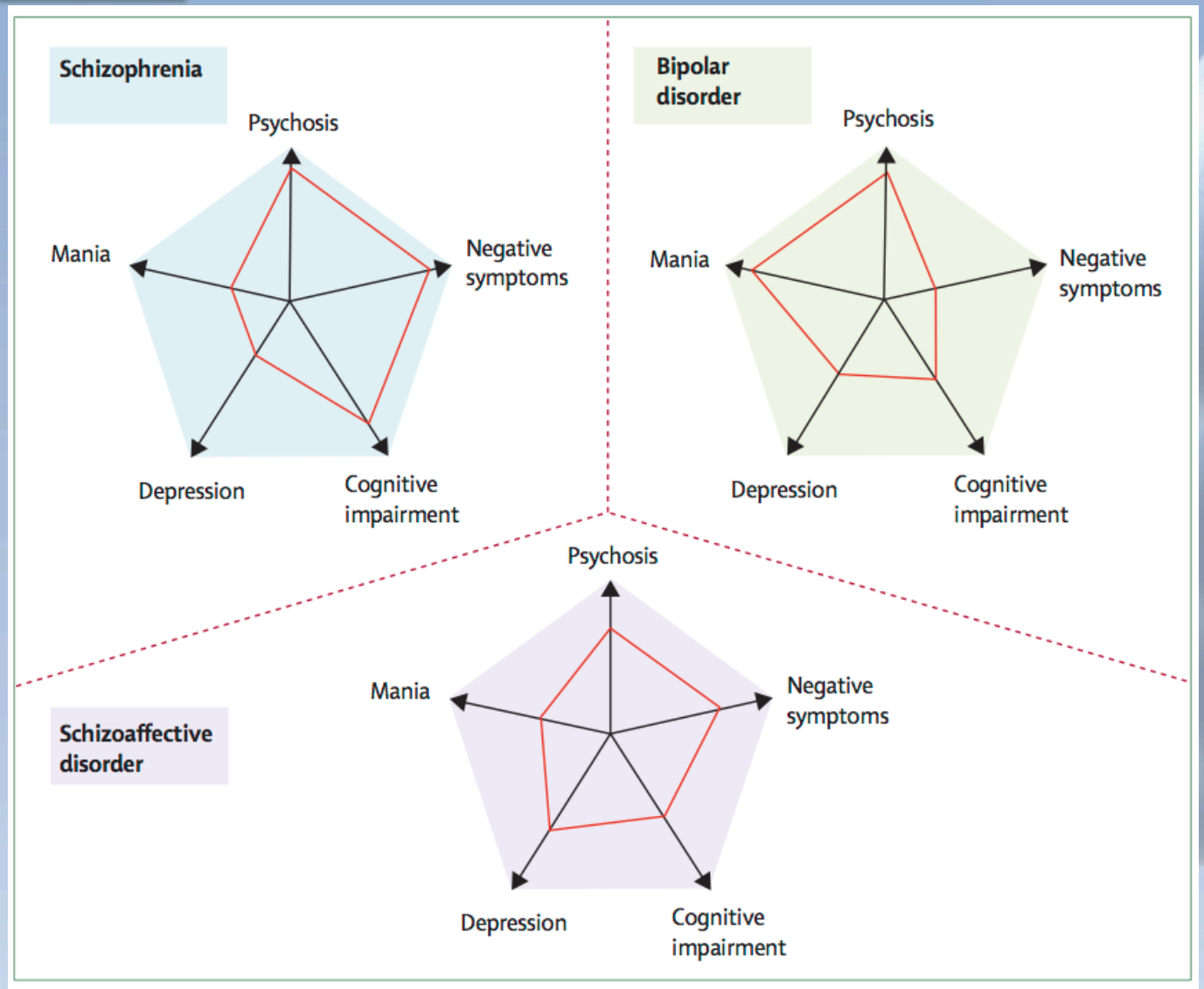
Historical Perspective



Historical Perspective



Domains of Psychopathology



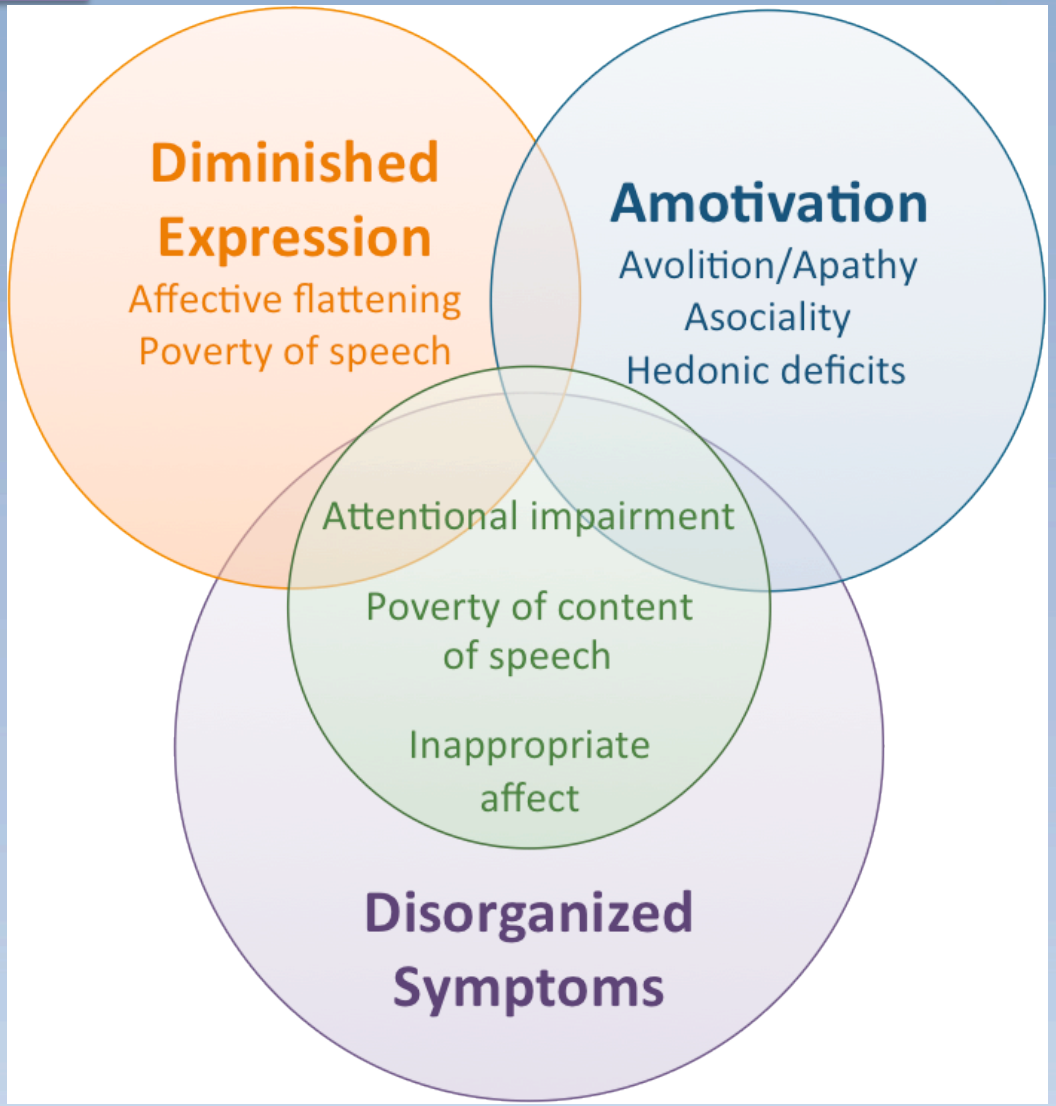
van Os & Kapur 2009.

The Negative Symptoms

- Affective flattening
- Alogia
- Asociality
- Avolition
- Anhedonia

1) Andreasen 1982; 2) Kirkpatrick 2006.

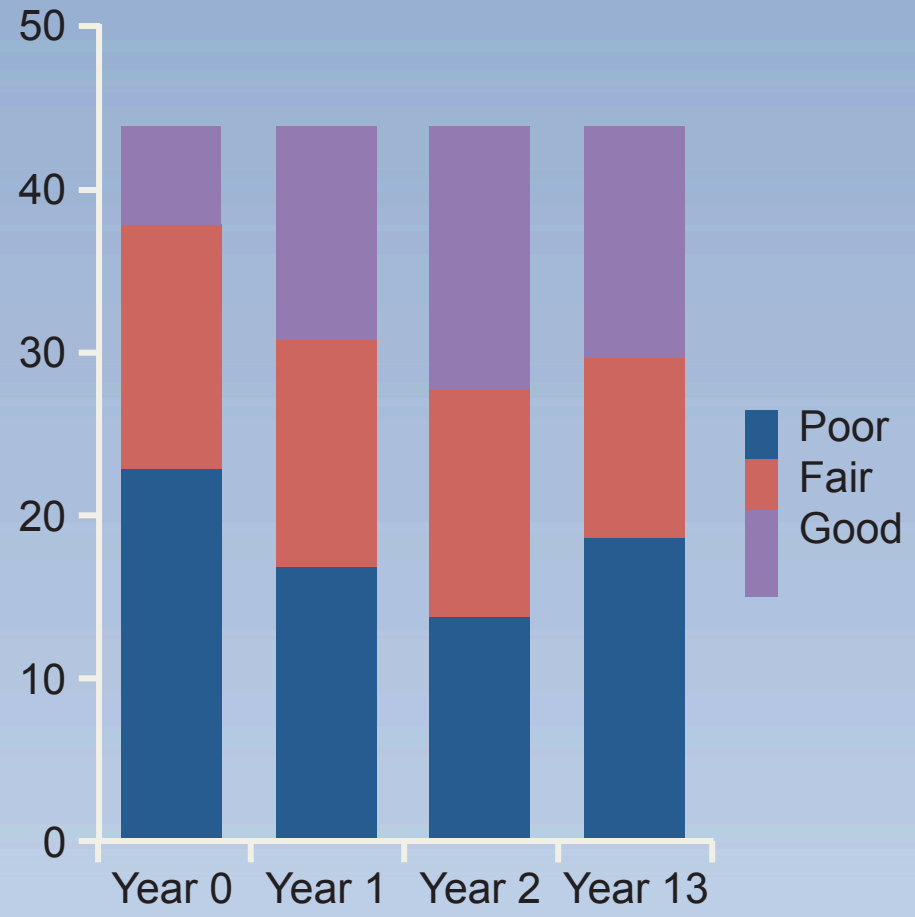
The Negative Symptoms



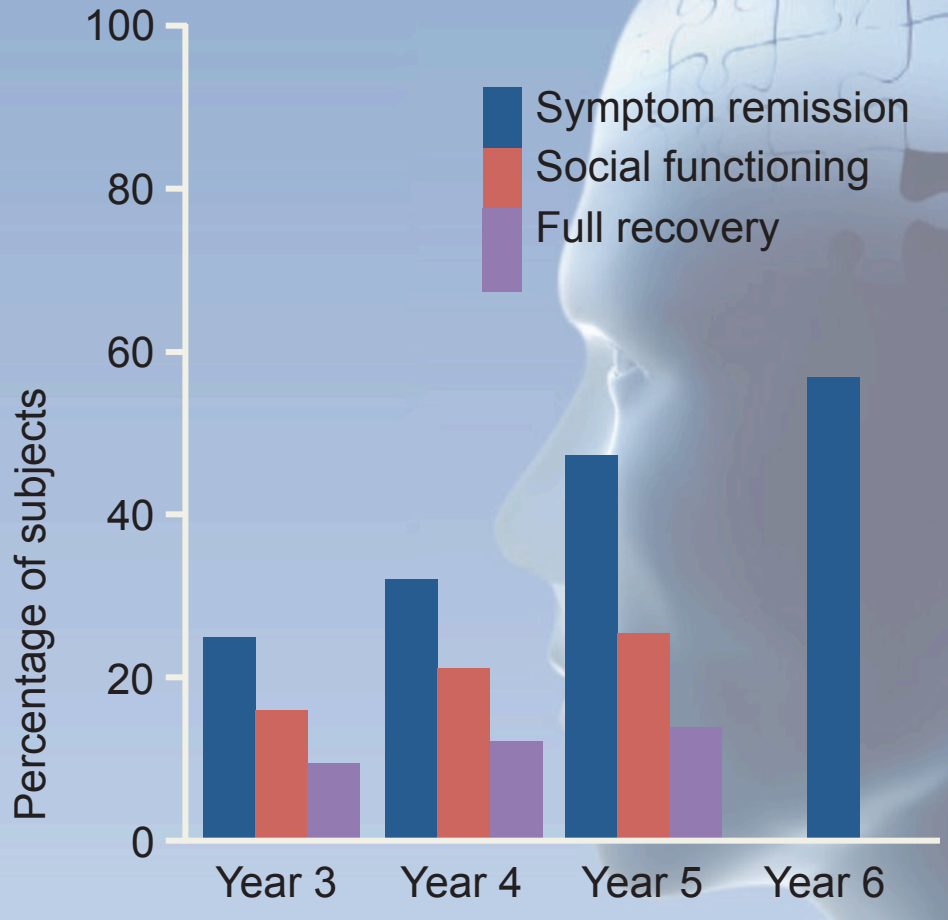
Mueser et al. 1994
Sayers et al. 1996
Kelley et al. 1999
Peralta & Cuesta 1999
Kimhy et al. 2006
Foussias & Remington 2010
Messinger et al. 2011
Liemburg et al. 2013
Strauss et al. 2013
Fervaha et al. 2014

Functional Outcomes in Schizophrenia

WHO-ISOS
Social adjustment over 13 years[1]



Cumulative Recovery Rates in First-Episode Schizophrenia[2]



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1. Mason et al. 1996; 2. Schooler 2006.

Functional Outcomes in Schizophrenia

Article

Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: A Longitudinal First-Episode Study With 7-Year Follow-Up

Peter Milev, M.D., Ph.D.
Beng-Choon Ho, M.R.C.Psych.
Stephan Arndt, Ph.D.
Nancy C. Andreasen, M.D., Ph.D.

Objective: The relationship between cognition and outcome in people with schizophrenia has been established in studies that, for the most part, examined chronic patients and were cross-sectional in design. The purpose of this study was to analyze the relationships between neurocognitive variables assessed at illness

Results: Verbal memory, processing speed and attention, and the severity of negative symptoms at intake were related to subsequent outcome. Global psychosocial functioning was predicted by negative symptoms and attention. Verbal memory was the significant predictor of the degree of impairment in recreational activities.

(Am J Psychiatry 2005; 162:495–506)

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Determinants of everyday outcomes in schizophrenia: The influences of cognitive impairment, functional capacity, and symptoms

Feea R. Leifker [a], Christopher R. Bowie [b], Philip D. Harvey [a,*]

Schizophrenia Bulletin vol. 31 no. 1 pp. 167–174, 2005
doi:10.1093/schbul/sbi004
Advance Access publication on February 16, 2005

Symptoms Versus Neurocognitive Test Performance as Predictors of Psychosocial Status in Schizophrenia: A 1- and 4-Year Prospective Study

Matthew M. Kurtz, Paul J. Moberg, J. Daniel Ragland, Ruben C. Gur, and Raquel E. Gur

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data

Jonathan Rabinowitz [a,*], Stephen Z. Levine [b], George Garibaldi [c], Dragana Bugarski-Kirola [c], Carmen Galani Berardo [c], Shitij Kapur [d]

Functional Outcomes in Schizophrenia

Schizophrenia Research 116 (2010) 20–26

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Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Apathy in first episode psychosis patients: One year follow up

Ann Faerden [a,*], Arnstein Finset [b], Svein Friis [a,c], Ingrid Agartz [c,d], Elizabeth Ann Barrett [e], Ragnar Nesvåg [d], Ole A. Andreassen [a,c], Stephen R. Marder [f,g], Ingrid Melle [a,c]

Psychiatry Research 210 (2013) 665–668

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

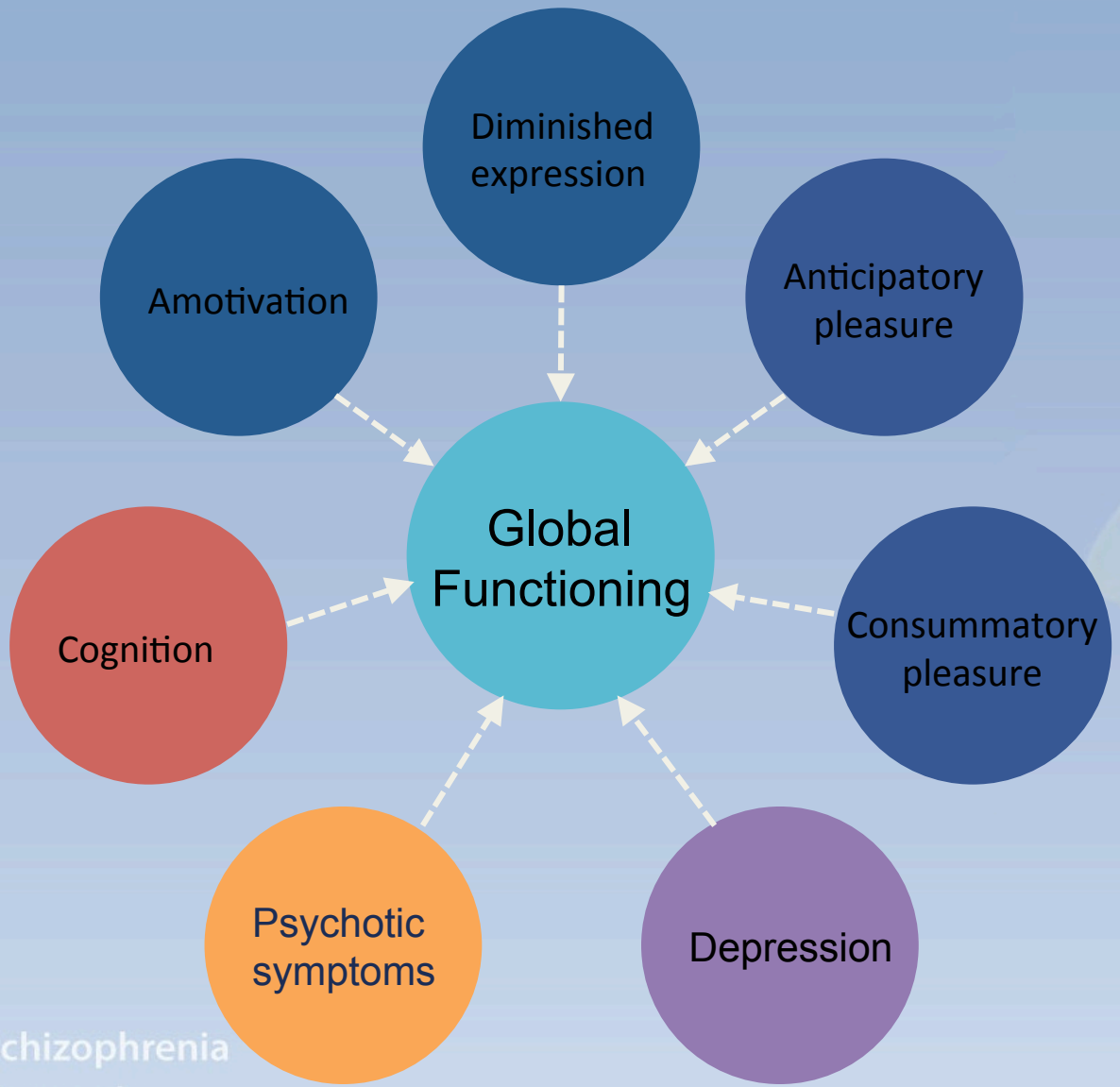
Amotivation and functional outcomes in early schizophrenia

Gagan Fervaha [a,b,*], George Foussias [a,b,c], Ofer Agid [a,c], Gary Remington [a,b,c]

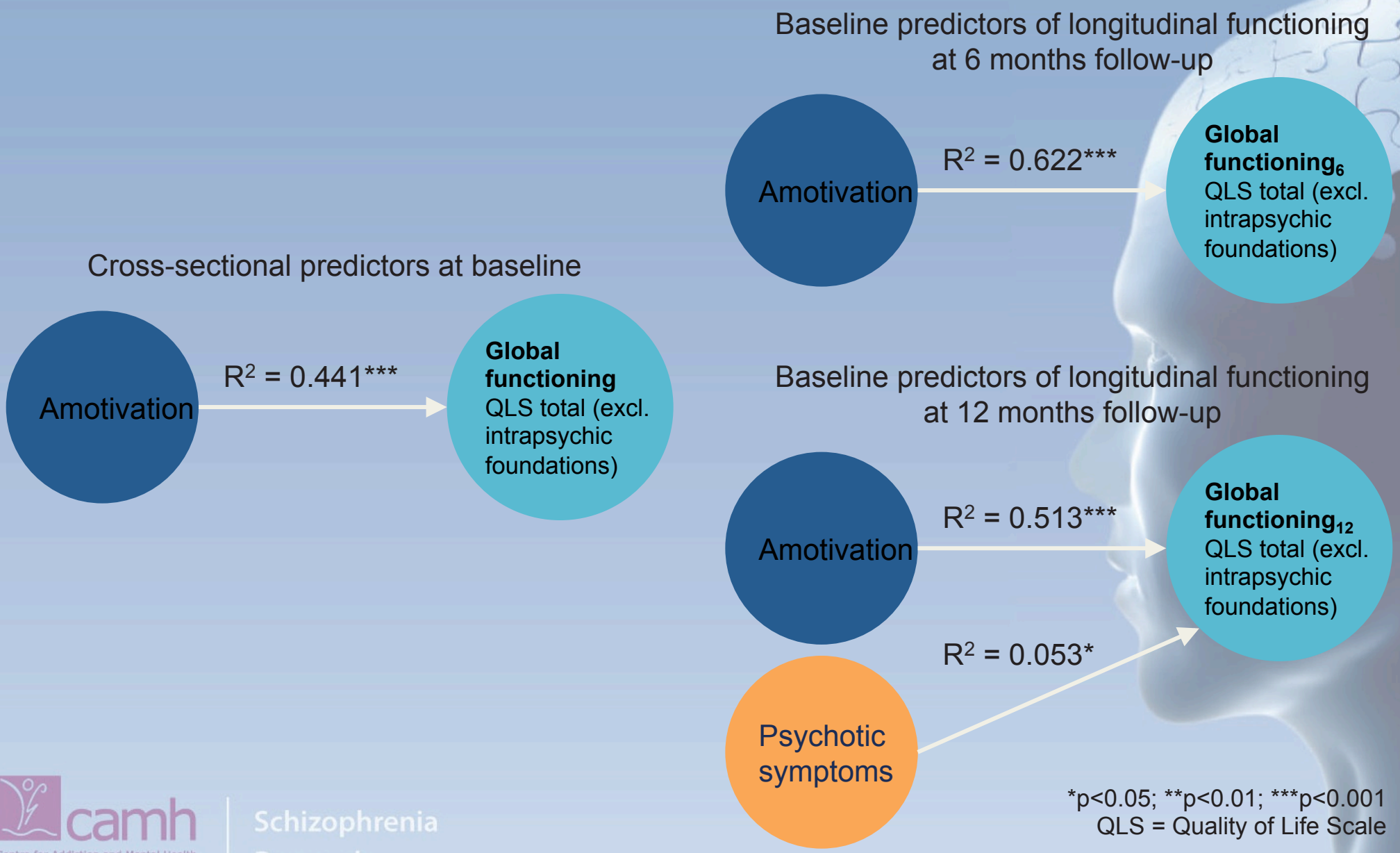
[a] Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, ON, Canada
[b] Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[c] Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Sayers et al. 1996; Kiang et al. 2003; Faerden et al. 2009 & 2010; Konstantakopoulos et al. 2011.

Predictors of Functional Outcomes in Schizophrenia



Predictors of Functional Outcomes in Schizophrenia



*p<0.05; **p<0.01; ***p<0.001
QLS = Quality of Life Scale

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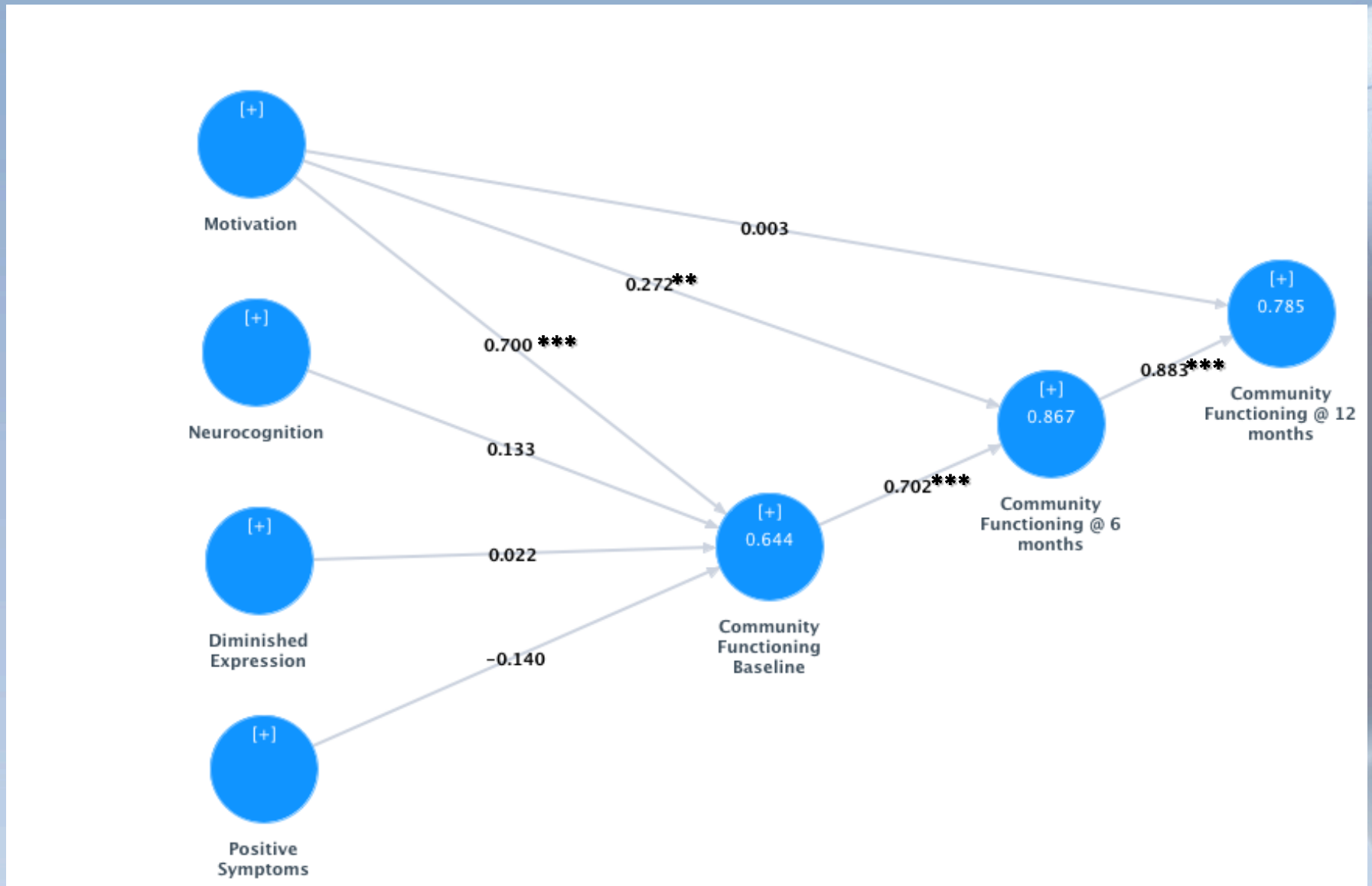
Foussias et al. 2009, 2011, and unpublished data

Pathways to Community Functioning in Schizophrenia



*p<0.05; **p<0.01; ***p<0.001

Foussias et al. 2015 (in preparation)

Cognitive Functioning and Motivational Deficits

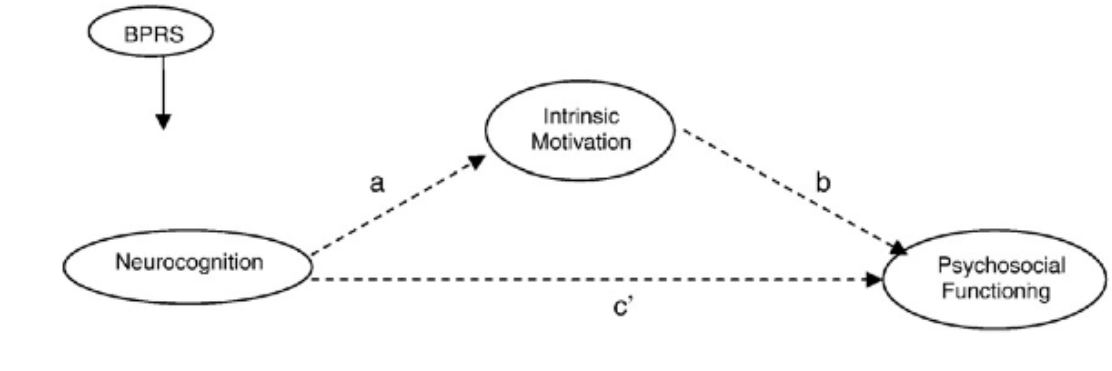
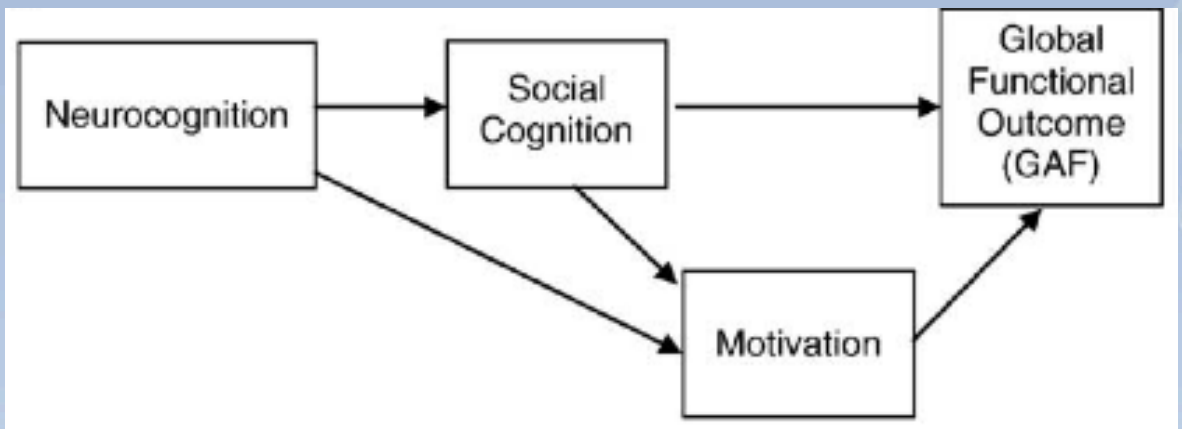


Fig. 1. Mediation model (controlling for psychiatric symptoms).



Nakagami et al. 2008; Gard et al. 2007 & 2009.

Cognitive Functioning and Motivational Deficits

- Impact of motivation on cognition?
  - Is poor performance on cognitive tasks due to lack of motivation to do well?

Barch 2005; Gorissen et al. 2005; Fervaha et al. 2014.

Cognitive Functioning and Motivational Deficits

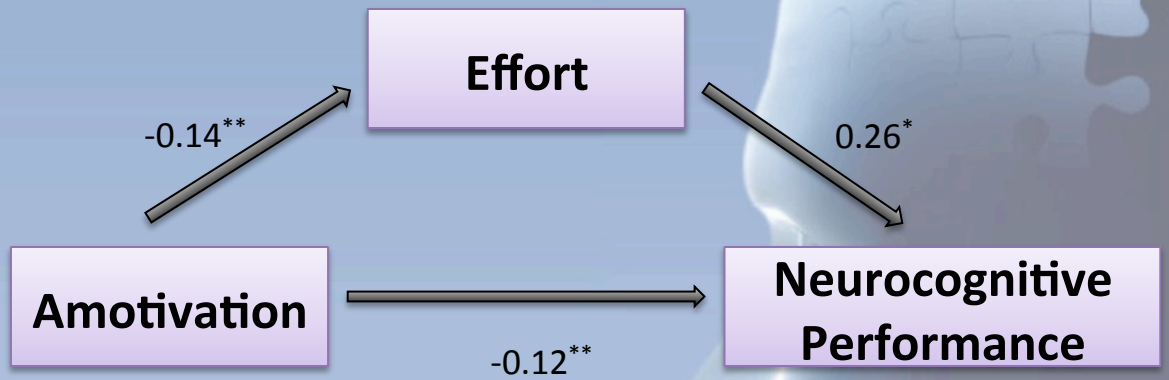
- Improved performance with monetary incentives
  - Executive function
  - Attention
  - Social cognition
- Effort testing
  - Insufficient effort in 10-25% of patients
  - Amotivation in the cognitive realm
  - Accounts for up to 1/3 of the variance in cognitive test performance

Barch 2005; Goldberg et al. 2007; Gorissen et al. 2005; Strauss et al. 2014.

Cognitive Functioning and Motivational Deficits

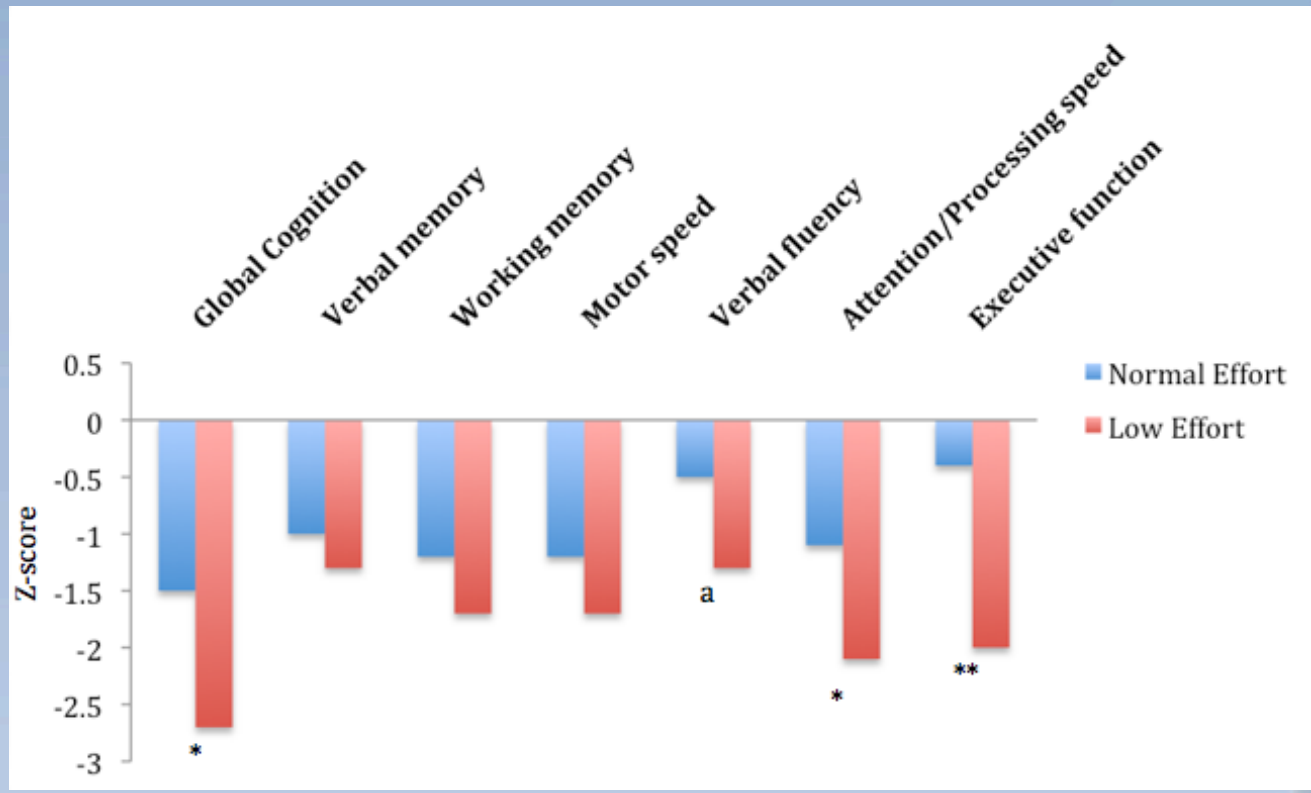
	Amotivation Composite Score (r)	Effort (TOMM) (r)
Effort (TOMM)	-.39**	
BACS Composite	-.43***	.39**
Verbal Memory	-.30*	ns
Working Memory	-.28*	.26*
Motor Speed	ns	ns
Verbal Fluency	-.49***	.41***
Attention/Processing Speed	-.25*	.30*
Executive Function	-.25*	.34**

ns. not significant; * p<.05; ** p<.01; *** p<.001; [a] p=.050; [b] p=.051.



Foussias et al. 2015 (under review)

Cognitive Functioning and Motivational Deficits



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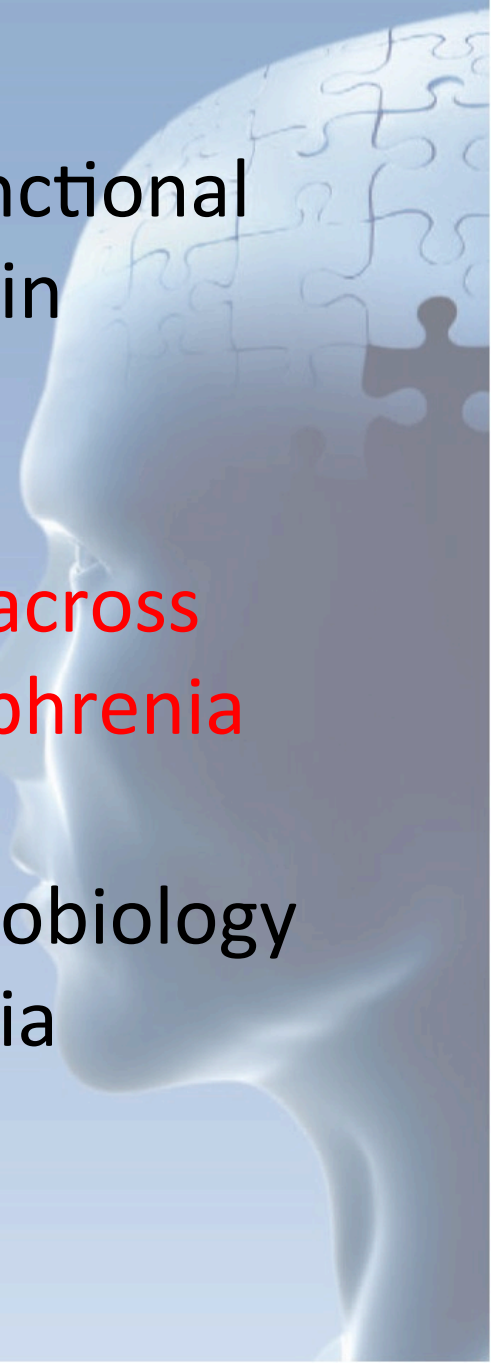
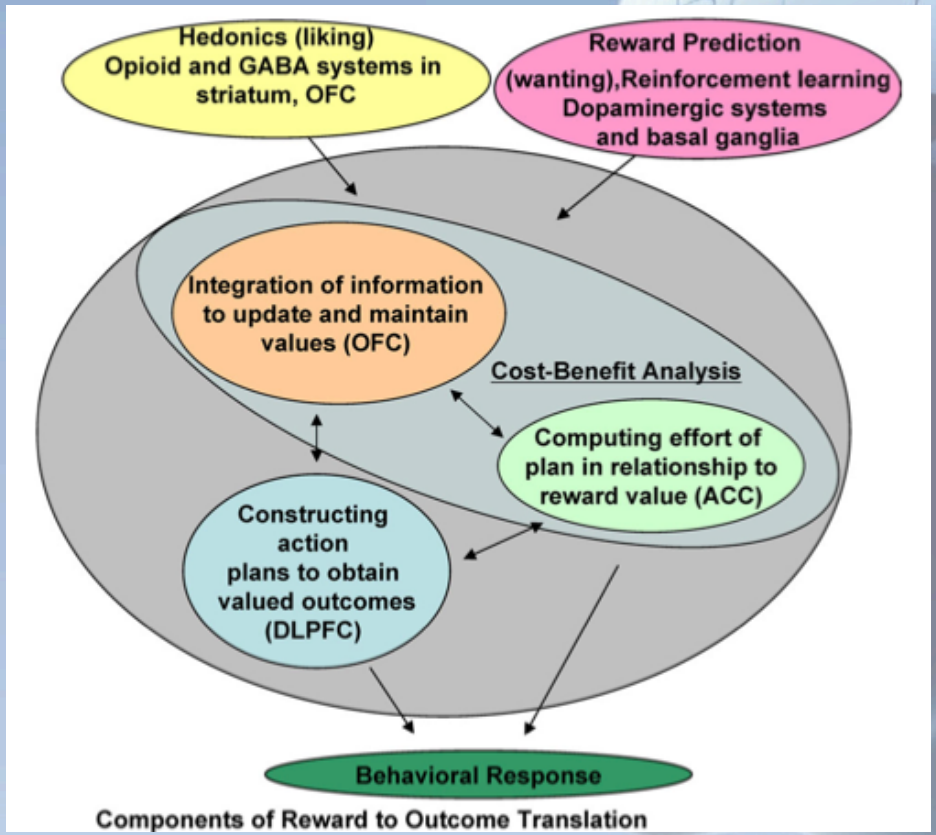


Motivation System Framework

- Multiple components to motivation:
  - hedonics or "liking"
  - reward prediction and "wanting"
  - cost-benefit analysis
  - generation and execution of goal-directed plans



Components of Reward to Outcome Translation

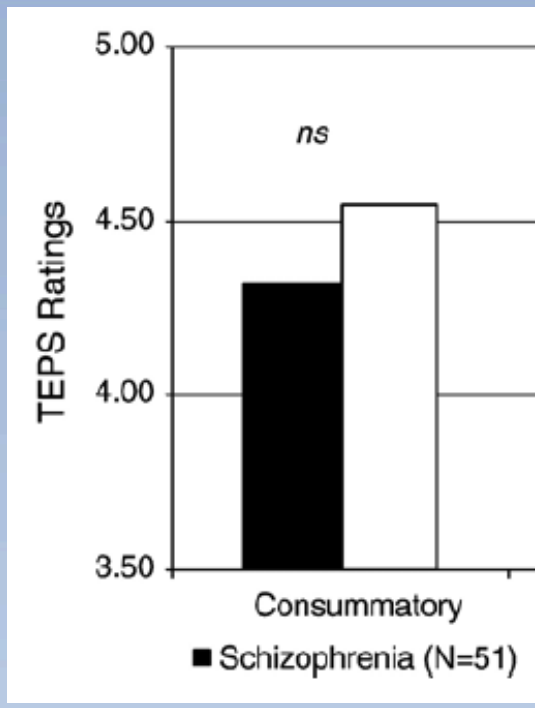
Barch and Dowd 2010

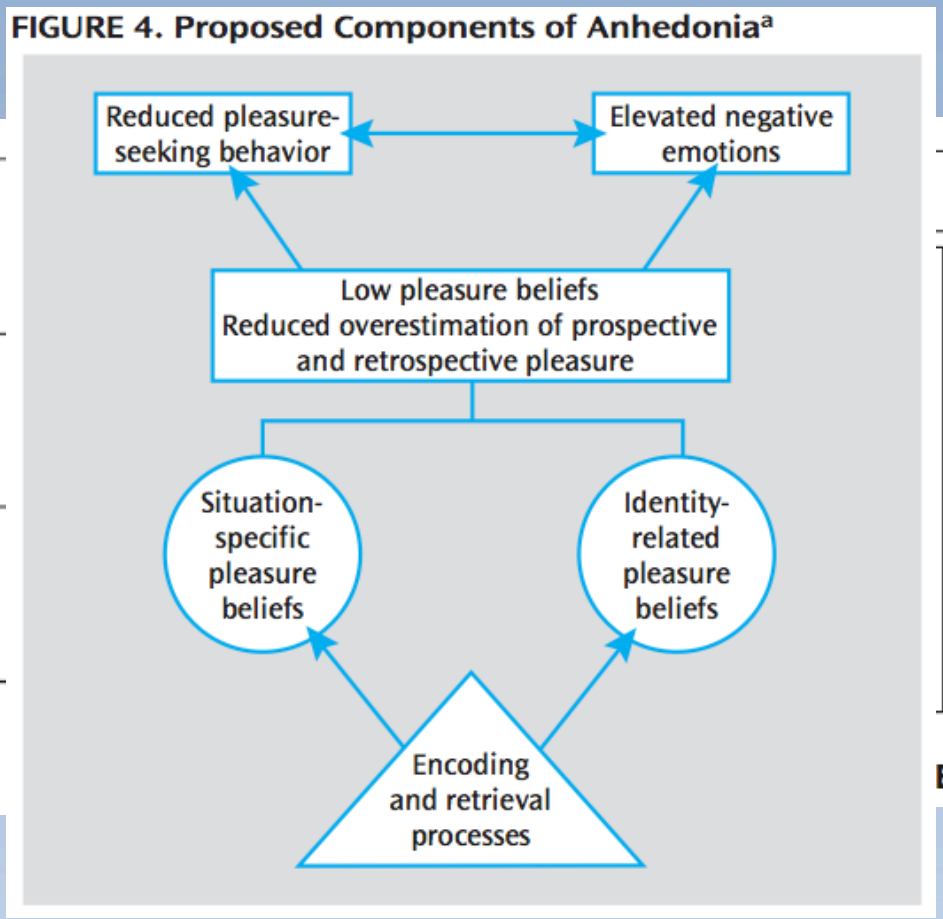
Hedonic Experience in Schizophrenia

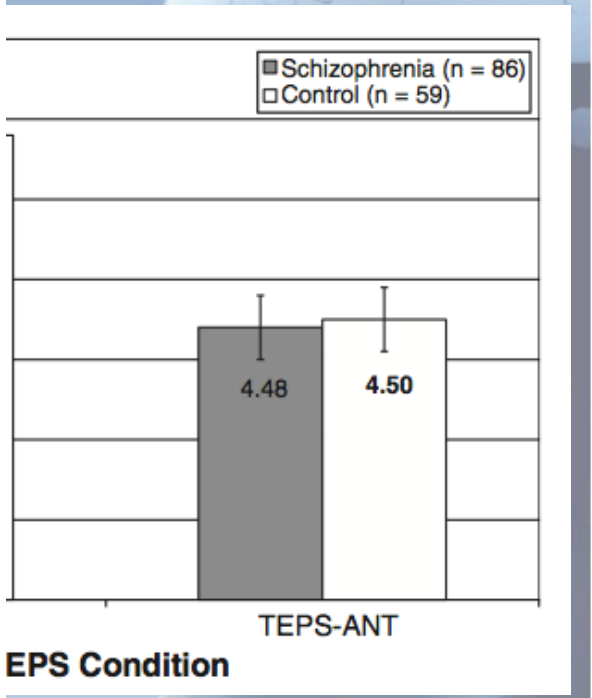
- Anhedonia
  - diminished capacity to experience interest or pleasure[1]

1) Andreasen 1984.

Hedonic Experience in Schizophrenia





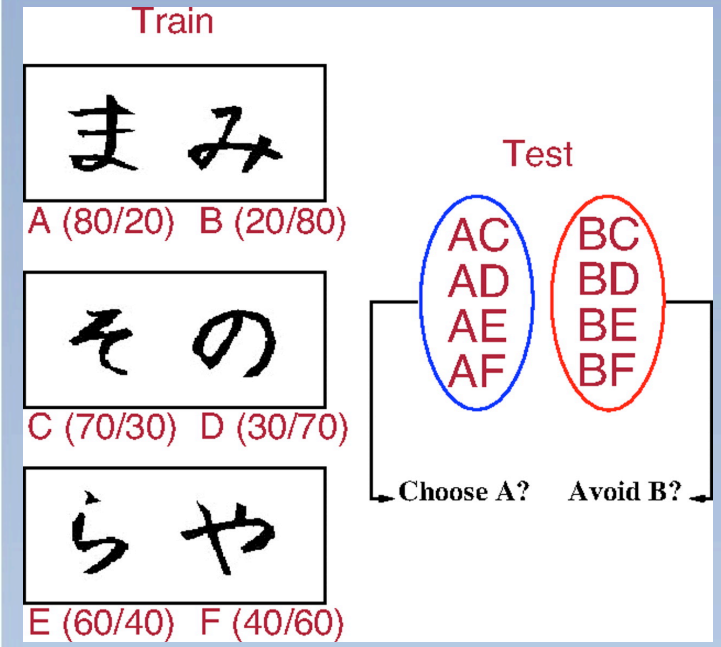


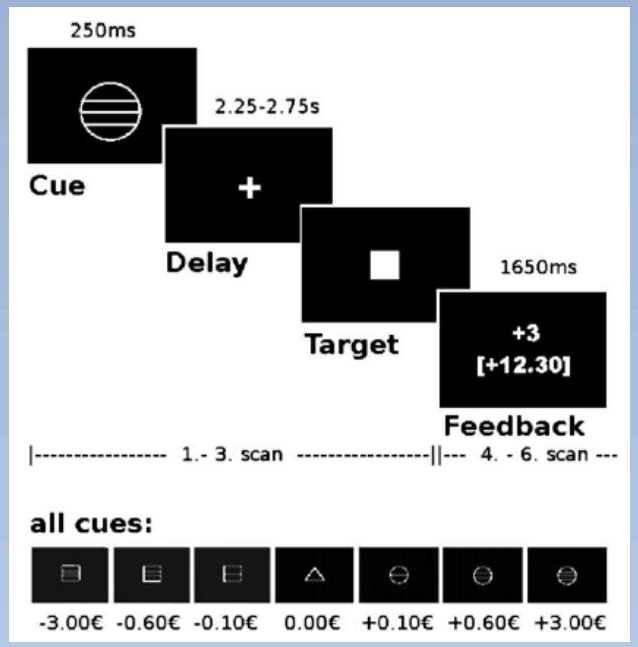
Gard et al. 2007; Strauss et al. 2011; Strauss et al. 2012.

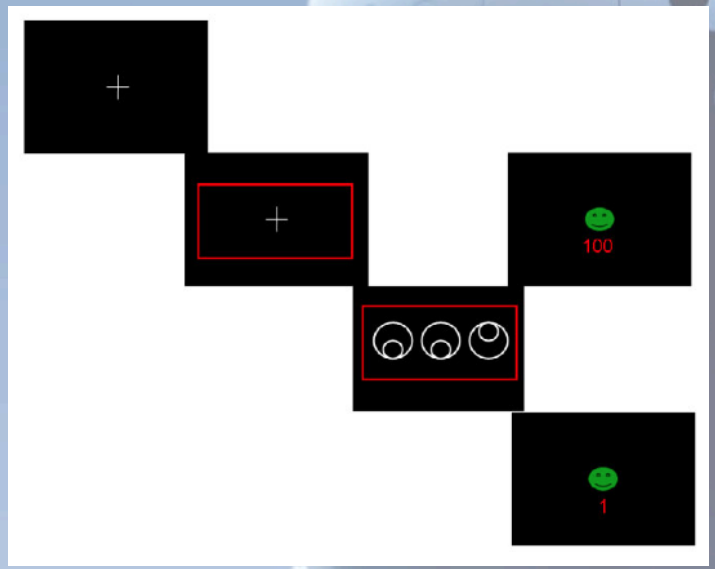
Hedonic Experience in Schizophrenia

Berenbaum & Oltmanns 1992; Burbridge & Barch 2007; Heerey & Gold 2007; Kring et al. 1993; Kring & Neale 1996; Earnst & Kring 1999; Cohen & Minor 2010.

Reward Prediction and "Wanting" in Schizophrenia

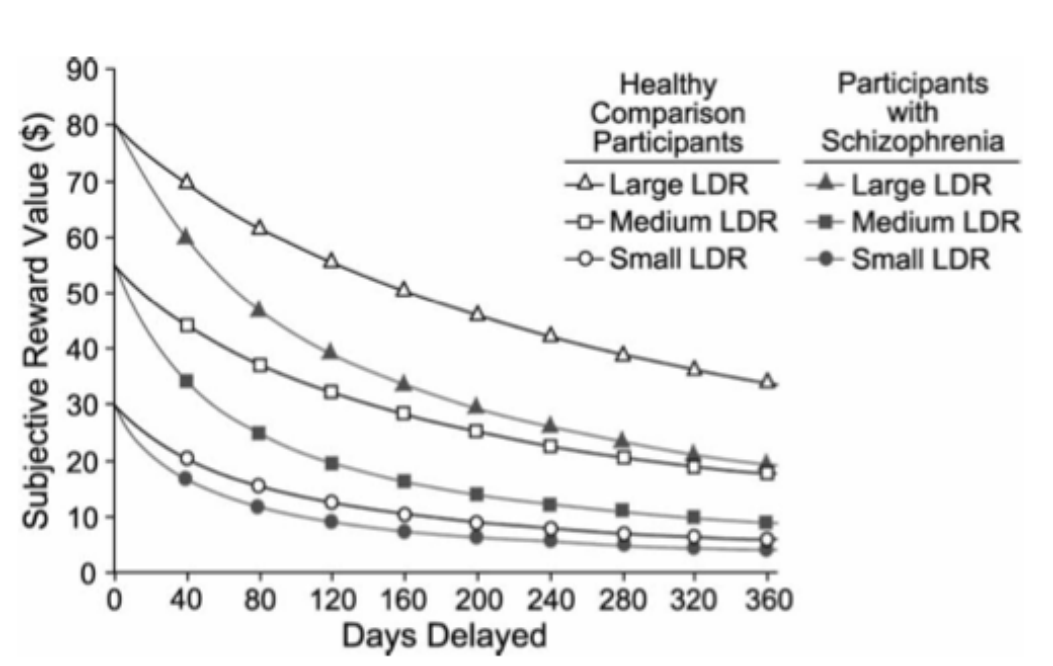


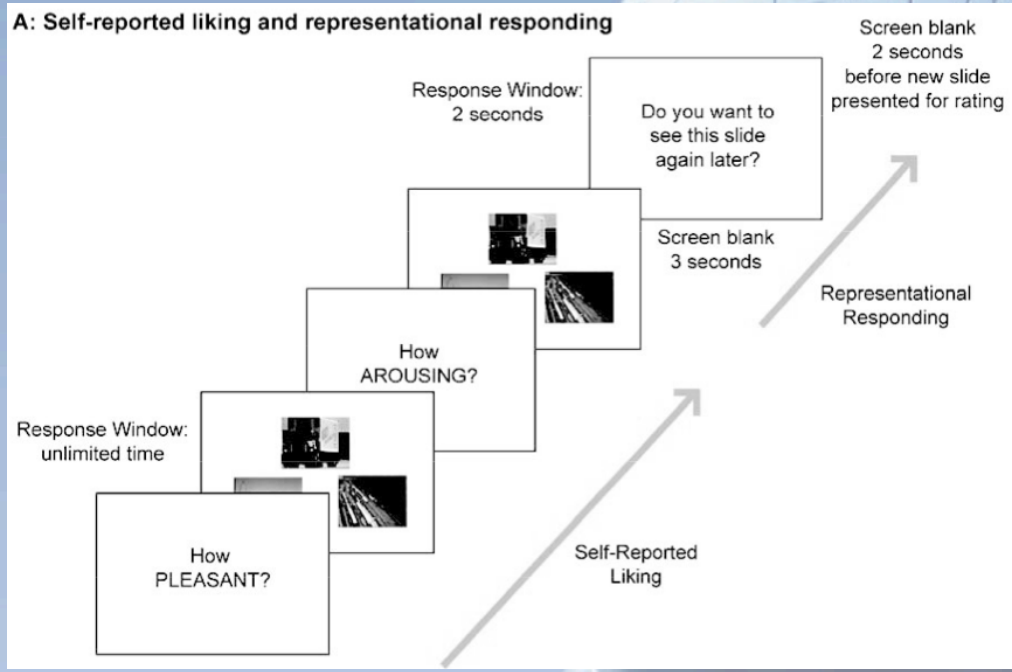




Waltz et al. 2007; Gold et al. 2008; Juckel et al. 2006; Murray et al. 2008.

Reward Valuation in Schizophrenia





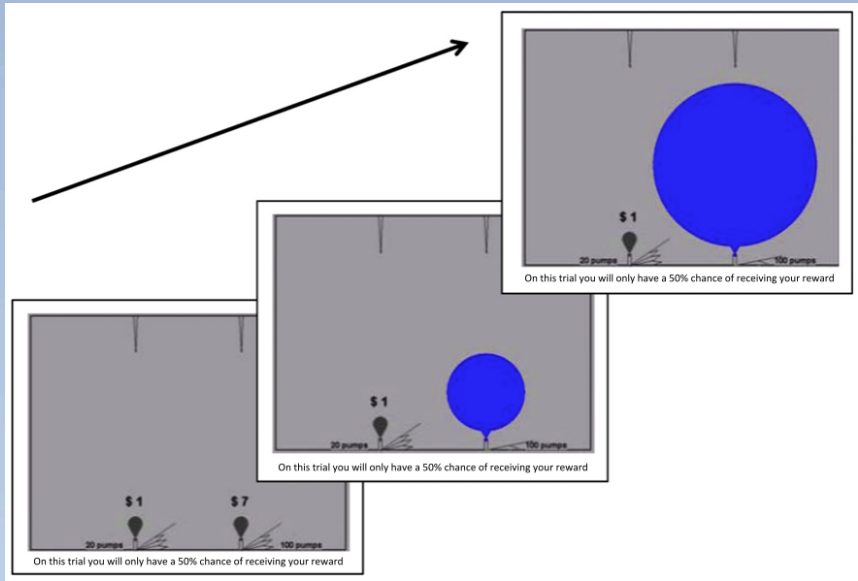
Heerey et al. 2007; Heerey et al. 2011; Heerey and Gold 2007.

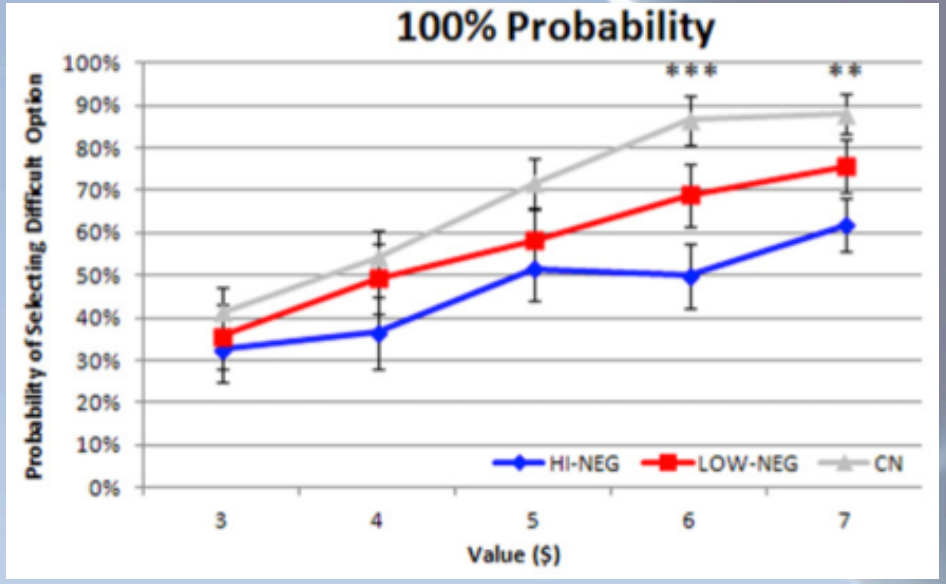
Effort Valuation in Schizophrenia

ARCHIVAL REPORT

Negative Symptoms of Schizophrenia Are Associated with Abnormal Effort-Cost Computations

James M. Gold, Gregory P. Strauss, James A. Waltz, Benjamin M. Robinson, Jamie K. Brown, and Michael J. Frank





Gold et al. 2013.

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Effort Valuation in Schizophrenia

Contents lists available at ScienceDirect

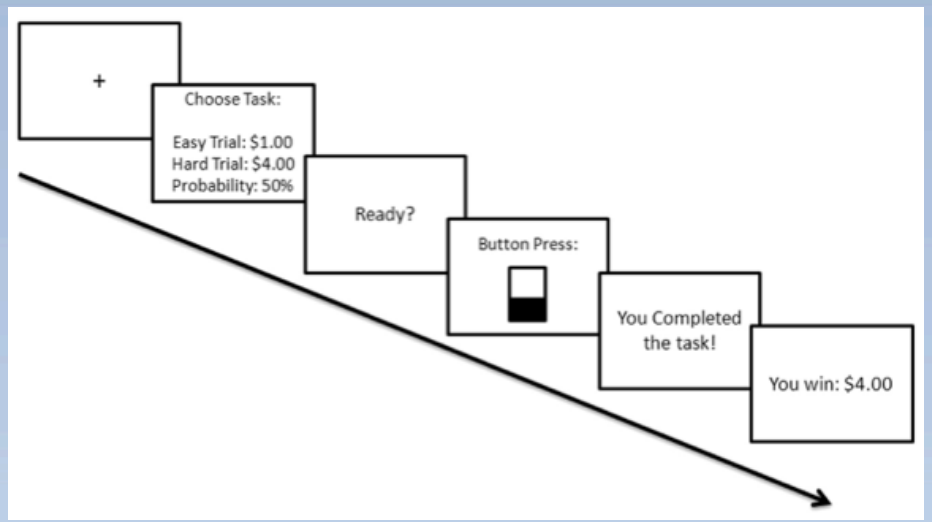
Journal of Psychiatric Research

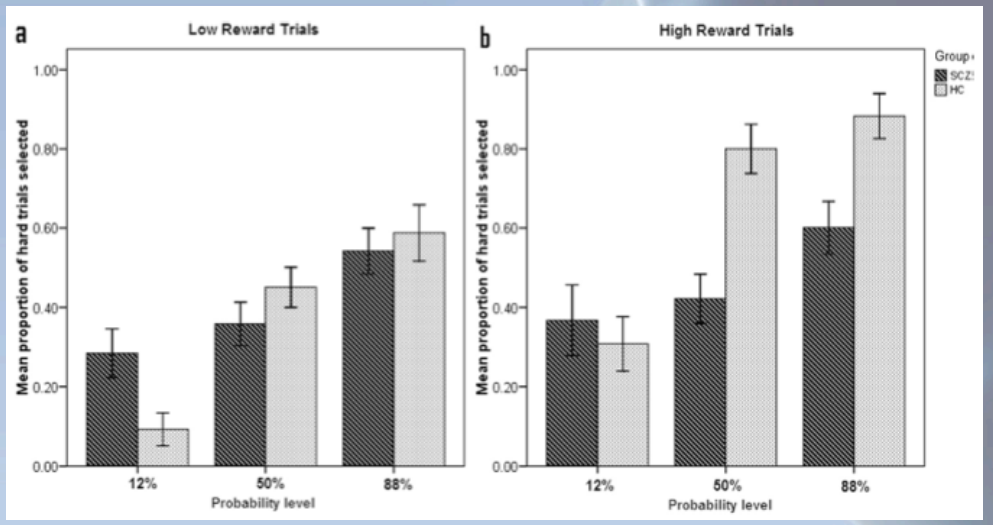
journal homepage: www.elsevier.com/locate/psychires

Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making

Gagan Fervaha [a,b,*], Ariel Graff-Guerrero [a,b,c], Konstantine K. Zakzanis [d], George Foussias [a,b,c], Ofer Agid [a,c], Gary Remington [a,b,c]

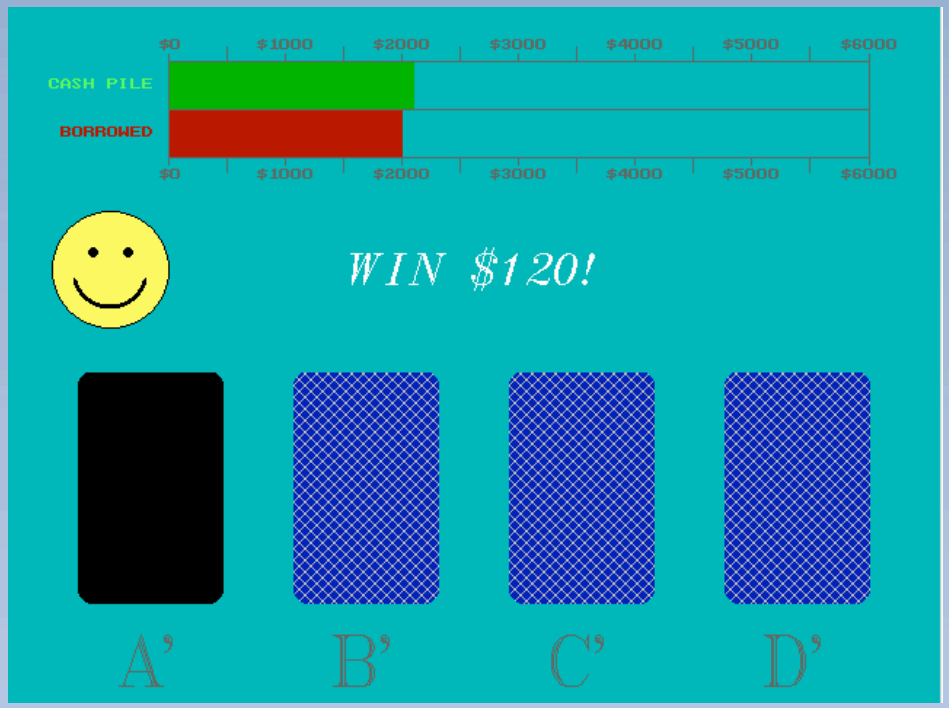
[a] Schizophrenia Division, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, Canada M5T 1R8
[b] Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[c] Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[d] Department of Psychology, University of Toronto Scarborough Campus, Toronto, ON, Canada

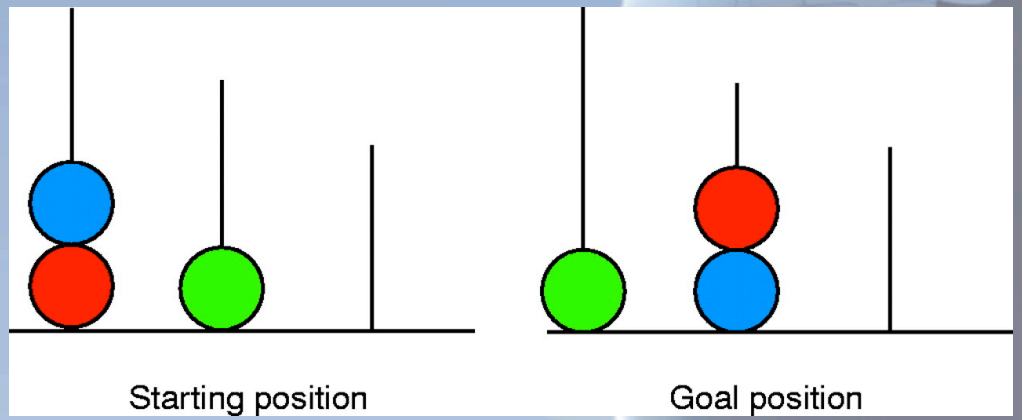




Fervaha et al. 2013.

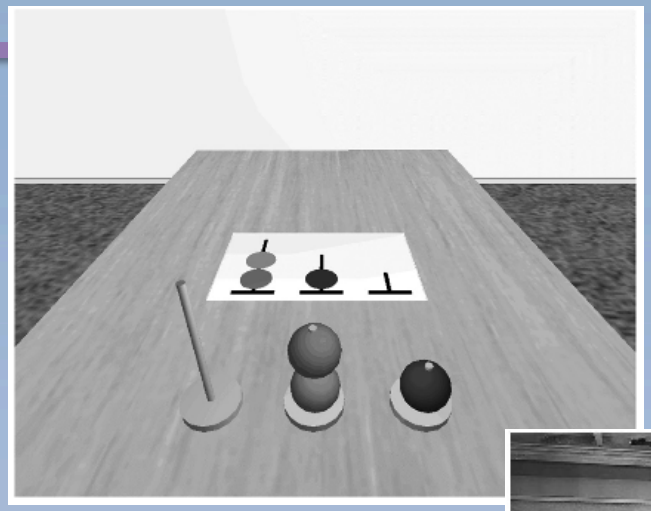
Goal-Directed Planning and Action in Schizophrenia



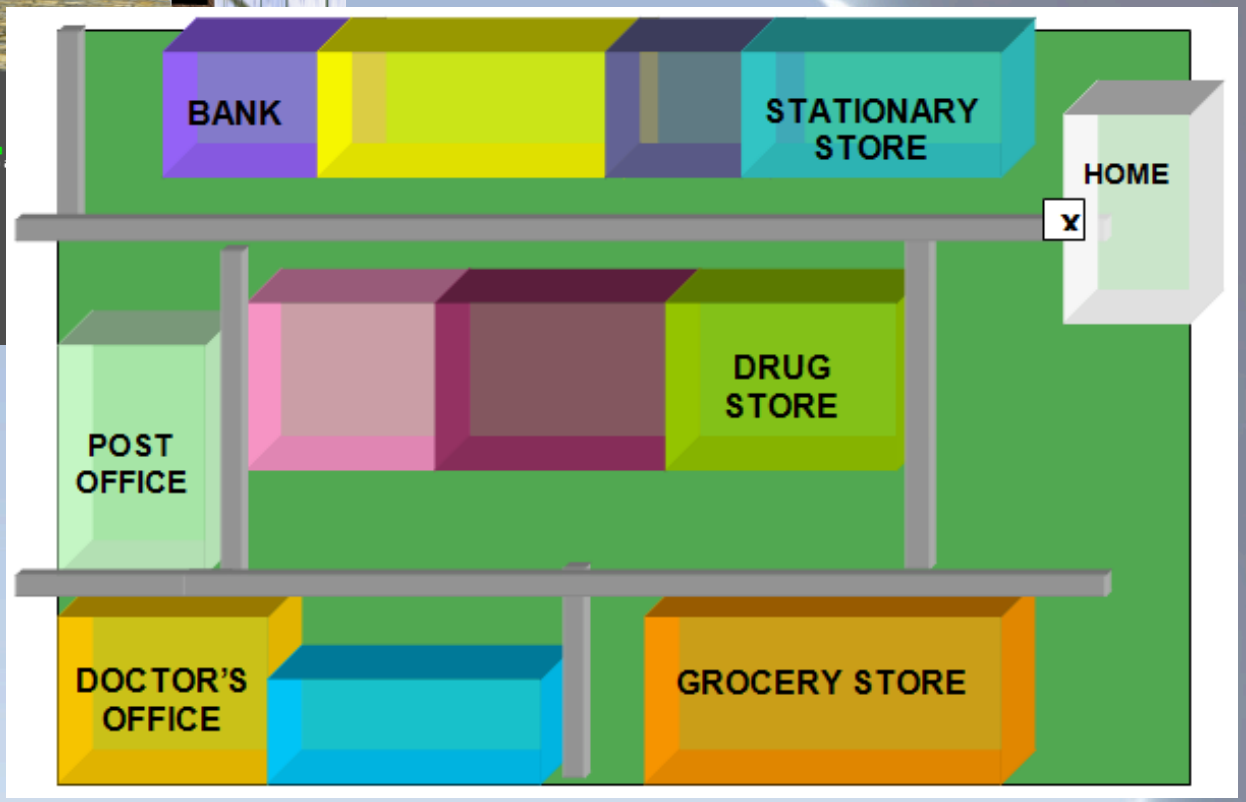


Fond et al. 2013; Kim et al. 2012; Heerey et al. 2008; Keefe et al.. 2004; Liemburg et al., 2015.

Virtual Reality and Ecological Validity



Goal-Directed Planning and Action



Jovanovski et al. 2012.

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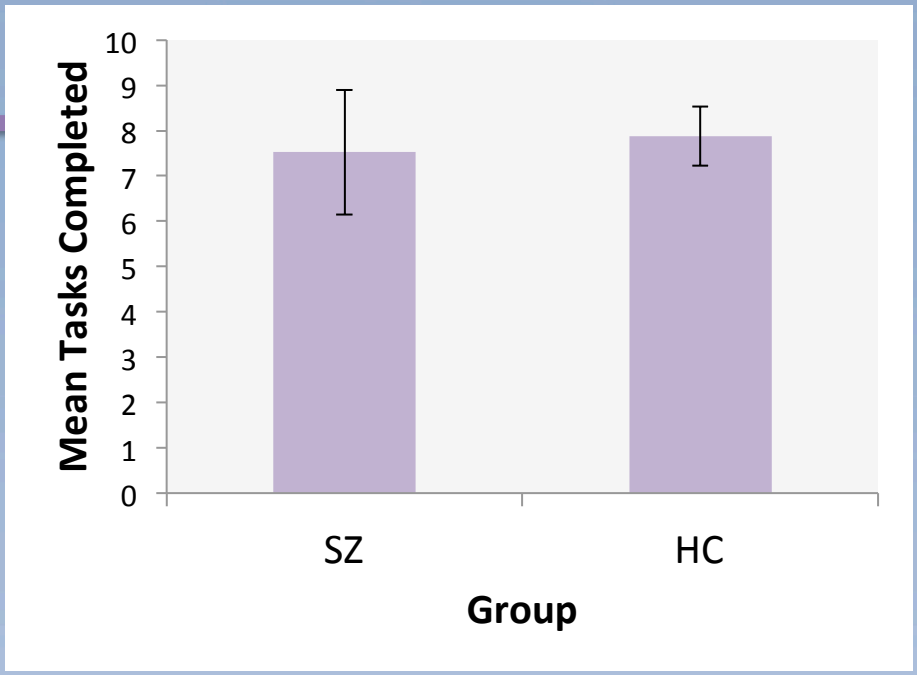
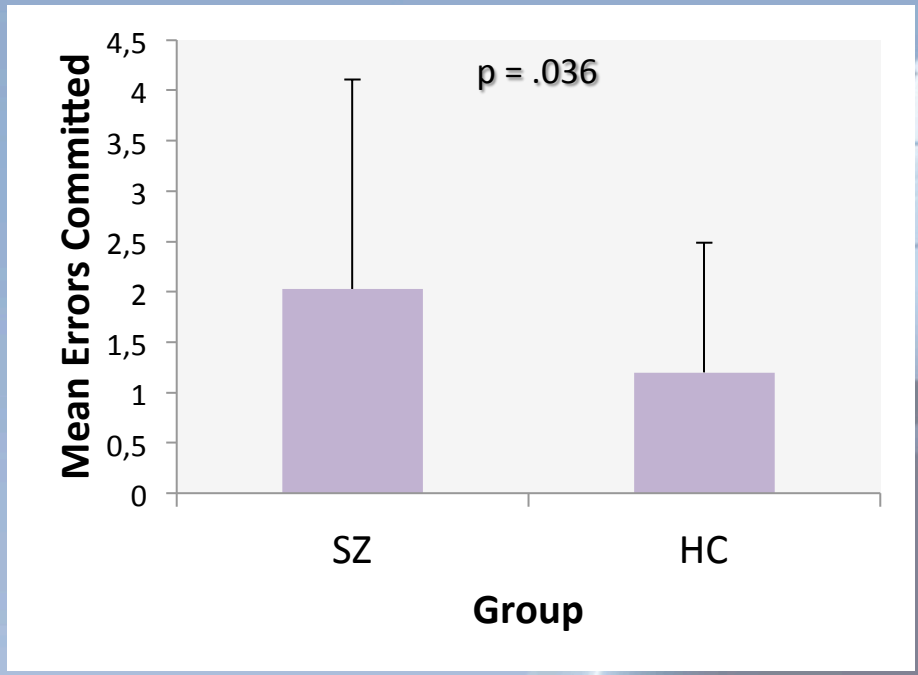
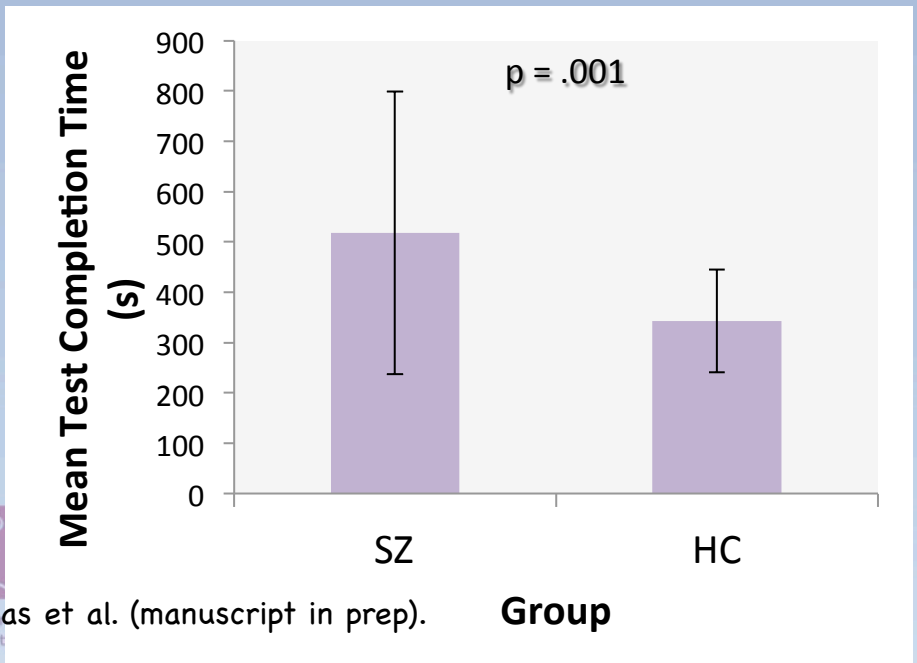
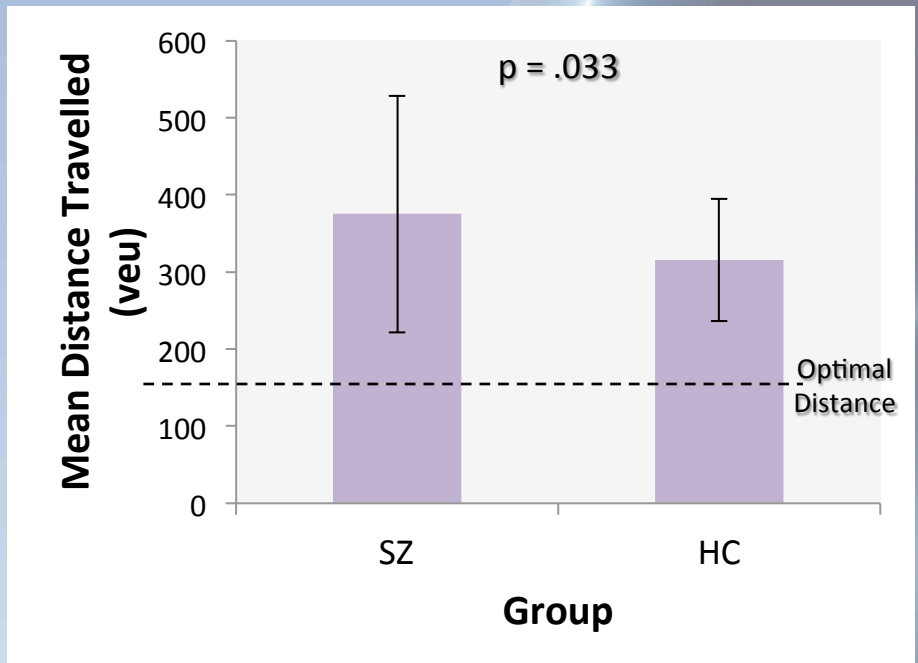
Goal-Directed Planning and Action









Foussias et al. (manuscript in prep).

Goal-Directed Planning and Action

Group Comparison

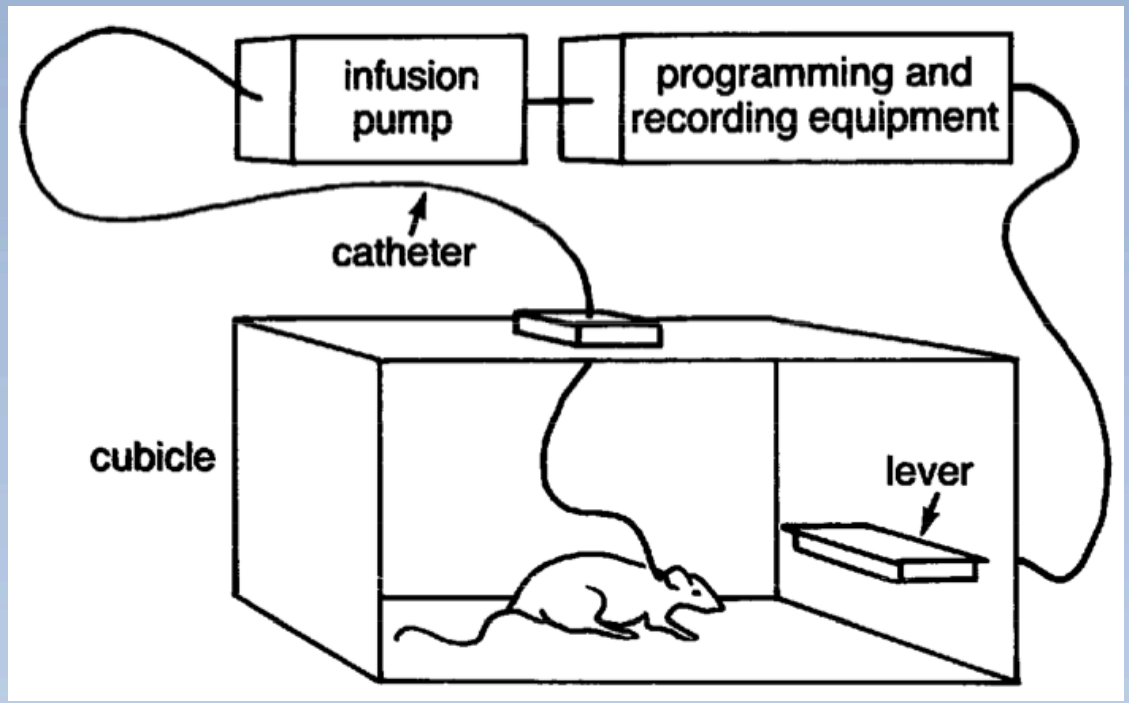
	SZ group (n=40) Mean (SD)	HC group (n=40) Mean (SD)	*t*	*p*	Effect Size (*d*)
Tasks Completed	7.5(1.4)	7.9(0.6)	1.45	ns	
Errors Committed	2.0(2.1)	1.2(1.3)	2.13	.036	0.48
Completion Time	518.0(290.7)	343.2(102.3)	3.70	.001	0.83
Distance Travelled	375.1(153.6)	315.4(79.2)	2.19	.033	0.49

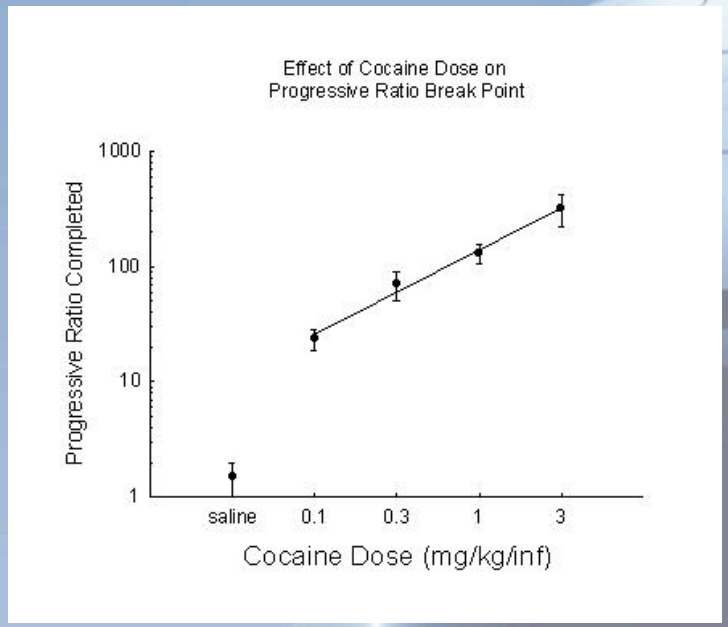
Bivariate Correlations (overall sample, n = 80)

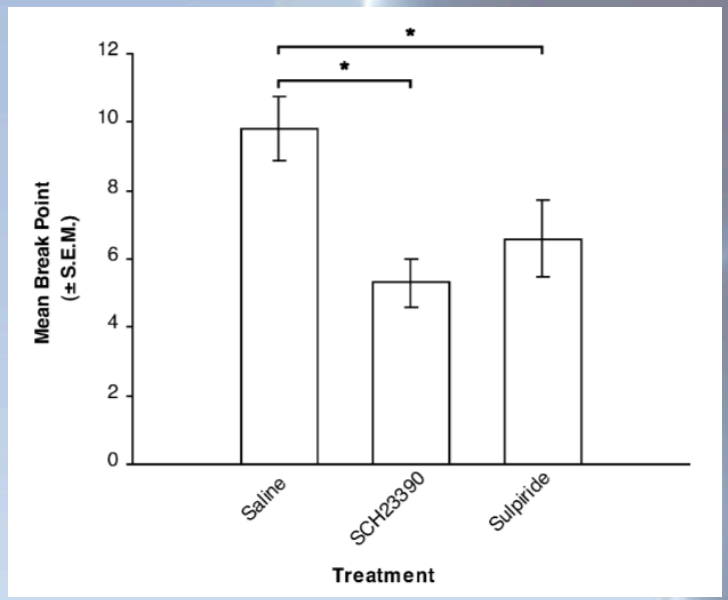
	Correlation (r)			
	Tasks Completed	**Errors Committed**	**Completion Time**	**Distance Travelled**
Intrinsic Motivation (QLS)	ns	-0.223*	-0.348**	-0.268*
Cognition (BACS Composite Z)	ns	-0.244*	-0.294**	-0.256*
Planning (BACS ToL)	ns	-0.233*	ns	ns
Motor Speed (BACS TMT)	ns	ns	ns	ns
Community Functioning (QLS)	ns	ns	-0.332**	-0.215$^{(p=0.055)}$

* $p < .05$; ** $p < .01$; ns – not significant

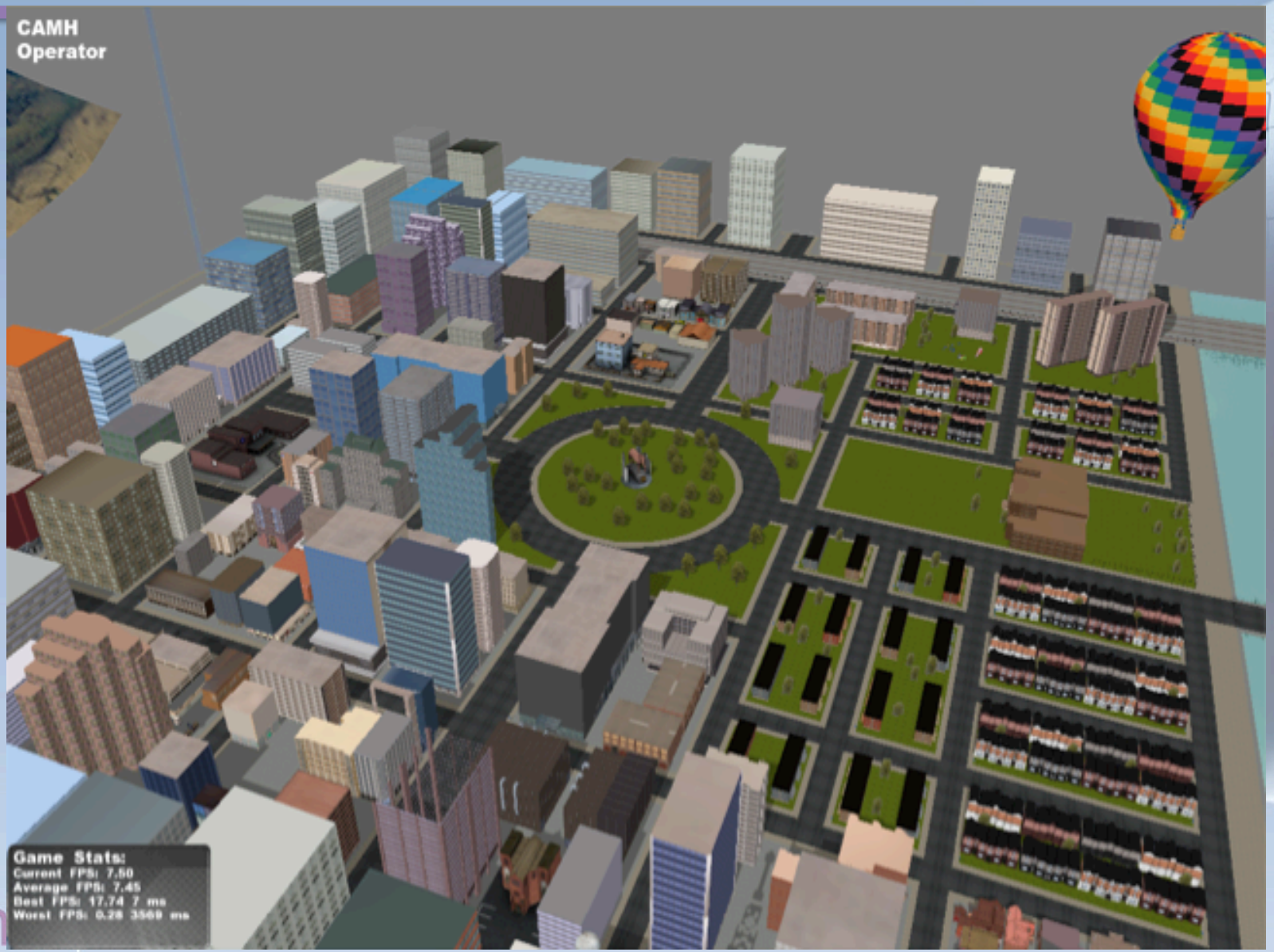
Animals At Work







Effort Valuation in a Virtual Environment (ViPR)

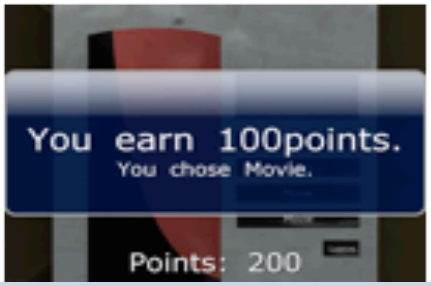


Effort Valuation in a Virtual Environment (ViPR)

Navigation to store

Task completion phase:
Progressively increasing effort requirement

Navigation to next store



Task completion phase:
points awarded

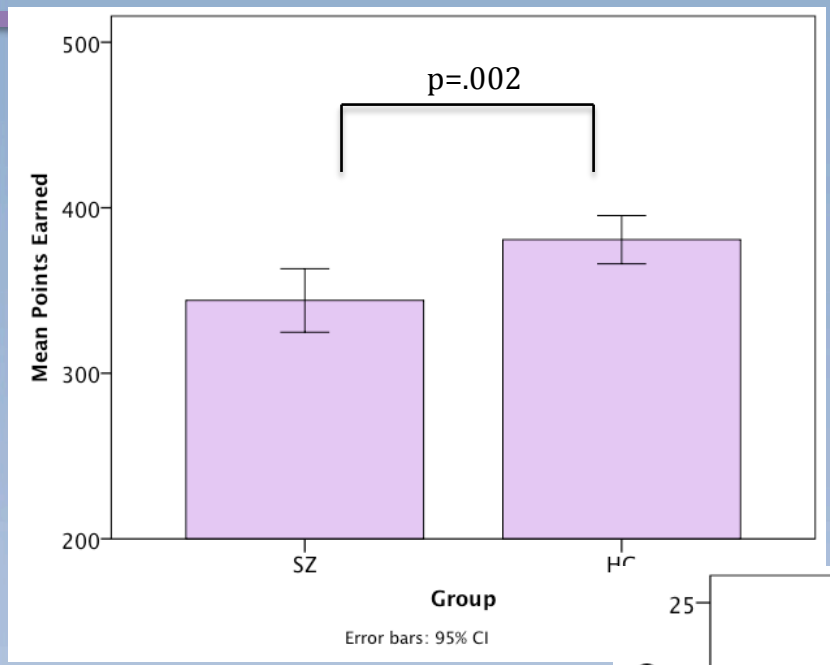
Effort Valuation in a Virtual Environment (ViPR)

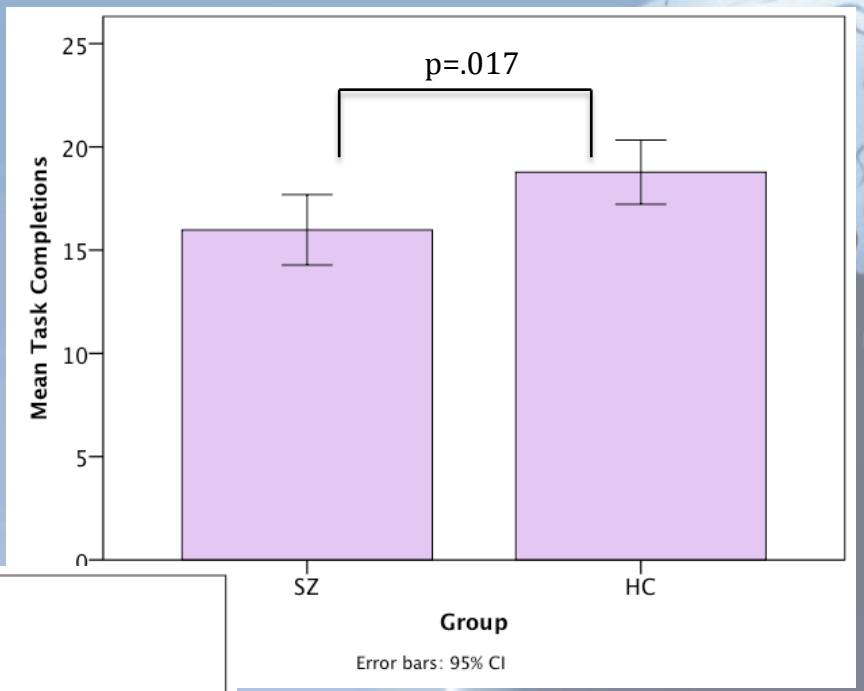
Demographics	SZ (n=50) Mean (SD)	HC (n=57) Mean (SD)	p
Age	36.9 (10.6)	35.8 (11.6)	ns
Sex (M:F)	31:19	35:22	ns
Diagnosis			
Schizophrenia	38		
Schizoaffective Disorder	12		
Duration of Illness (yrs)	13.6 (10.0)		

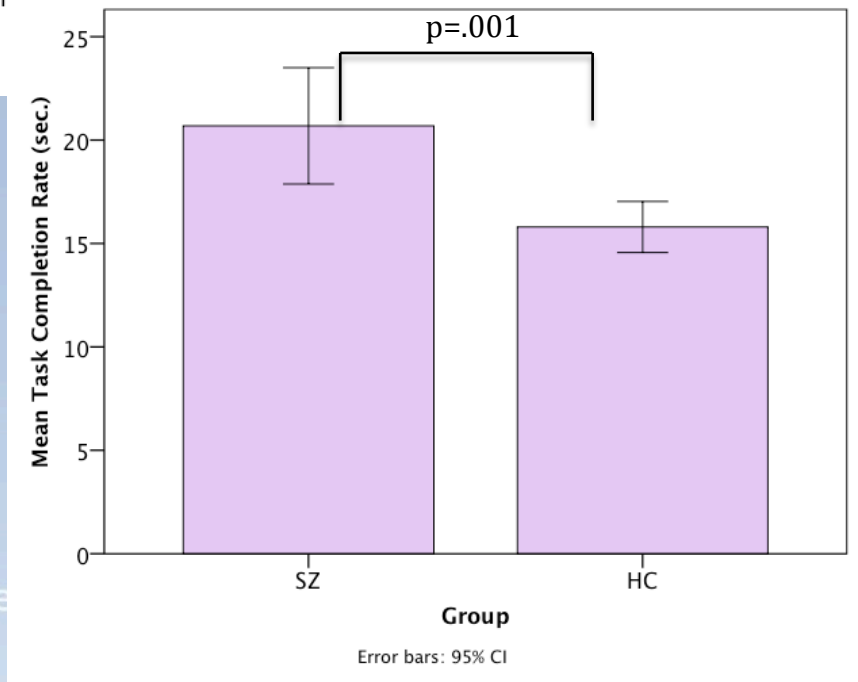
	Bivariate Correlations (rho)		
	Points Earned	**Task Completions**	**Task Completion Rate**
Amotivation (n=107)	- .26**	- .25**	.29**
SZ Only (n=50)			
Amotivation	- .29*	- .41**	.37**
Positive symptoms	-	-	-
Diminished Expression	-	-	-
Depression	-	-	-
Anticipatory Pleasure	-	-	-
Consummatory Pleasure	-	-	-
Neurocognition	-	-	-
Motor speed	-	-	-

* p<.05; ** p<.01.

Effort Valuation in a Virtual Environment (ViPR)





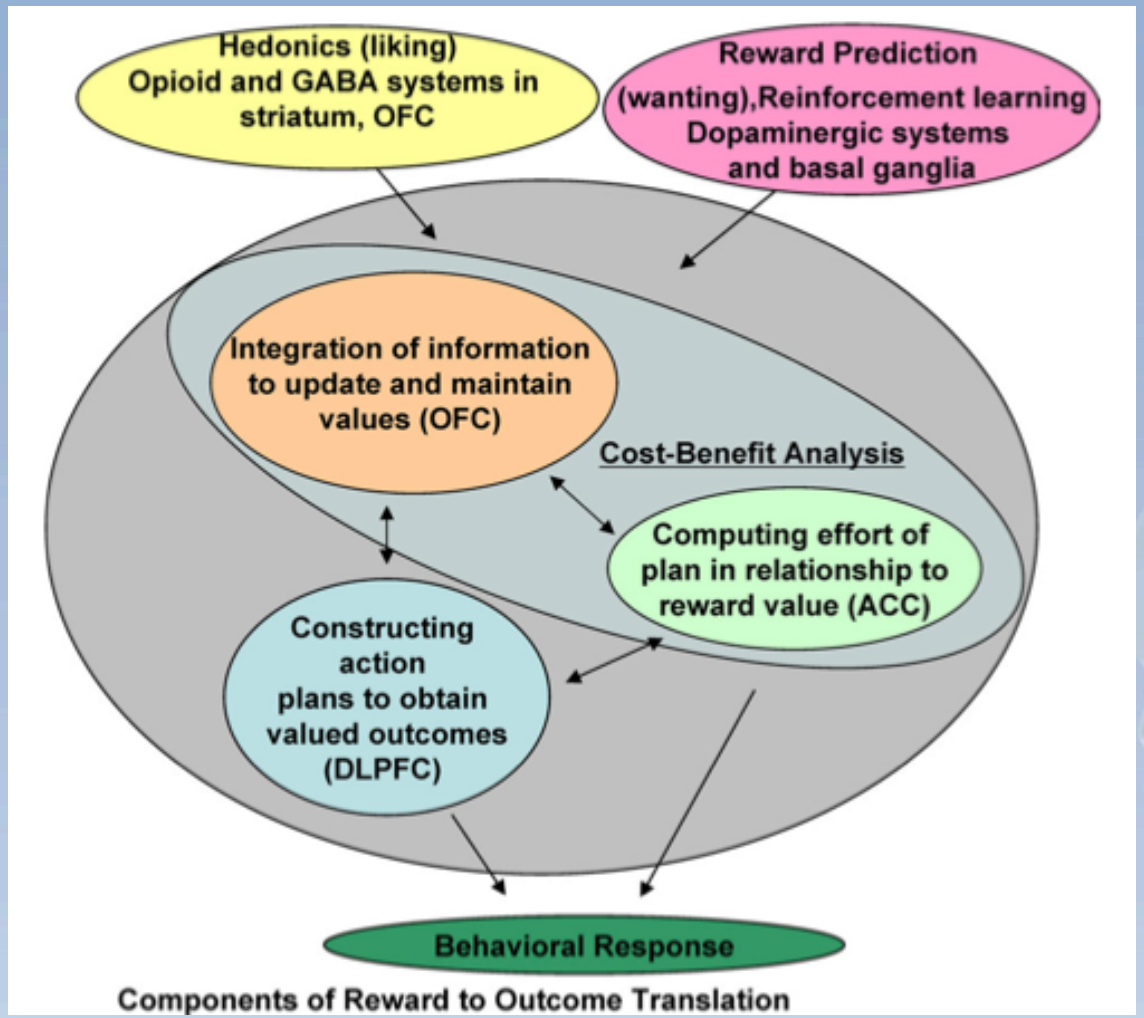


Foussias et al. 2015 (in preparation)

Objectives

- To review the phenomenology and functional consequences of motivational deficits in schizophrenia
- To examine behavioural impairments across discrete facets of motivation in schizophrenia
- To explore recent findings on the neurobiology of cost/effort valuation in schizophrenia

Motivation System Framework

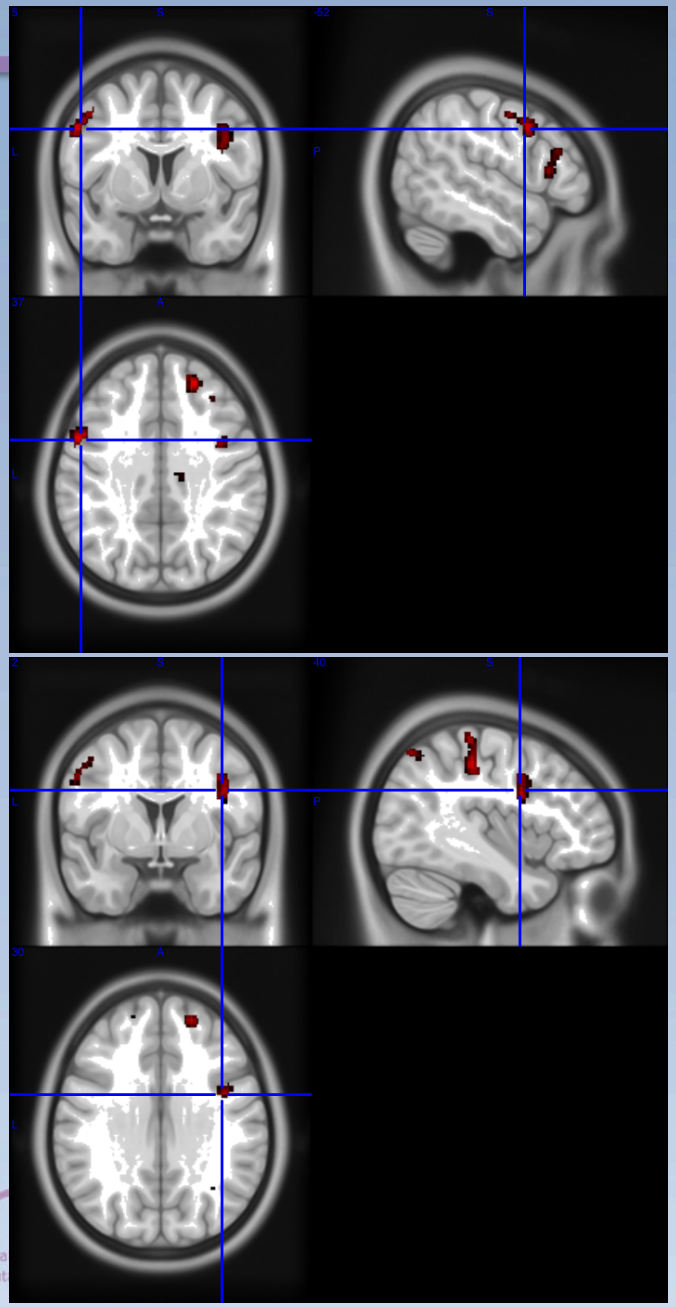


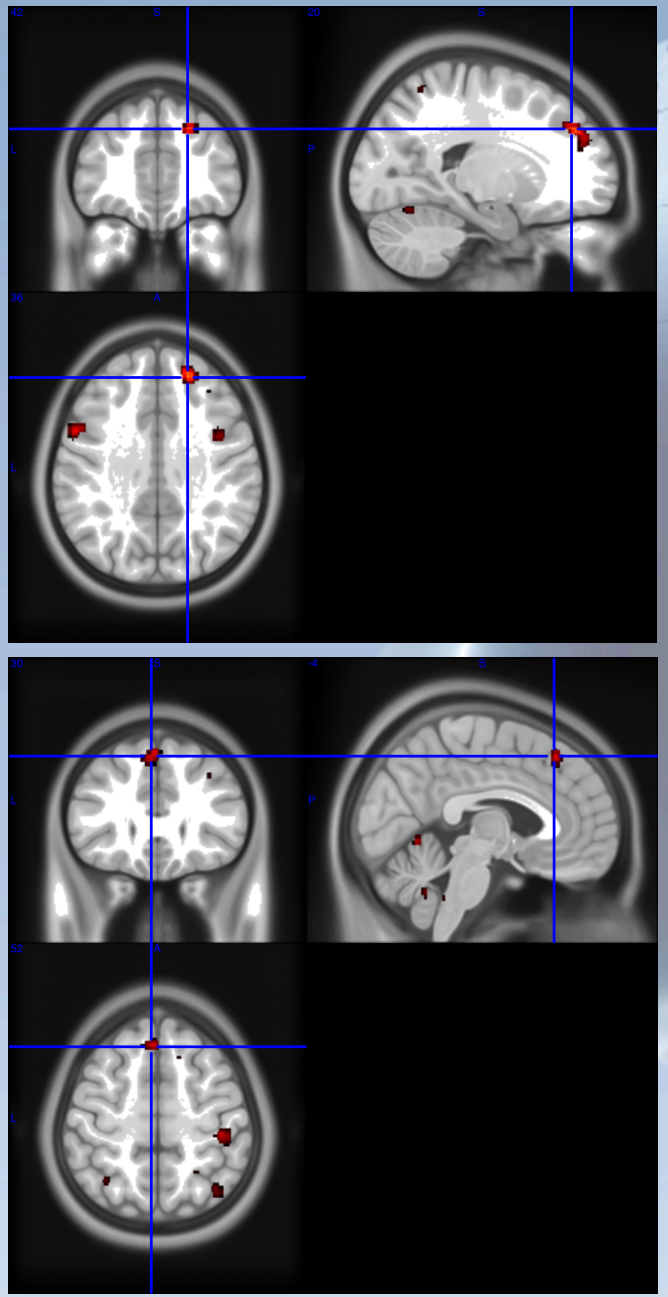
Components of Reward to Outcome Translation

Barch and Dowd 2010

The Neurobiology of Effort Valuation in a Virtual Environment

The Neurobiology of Effort Valuation in a Virtual Environment





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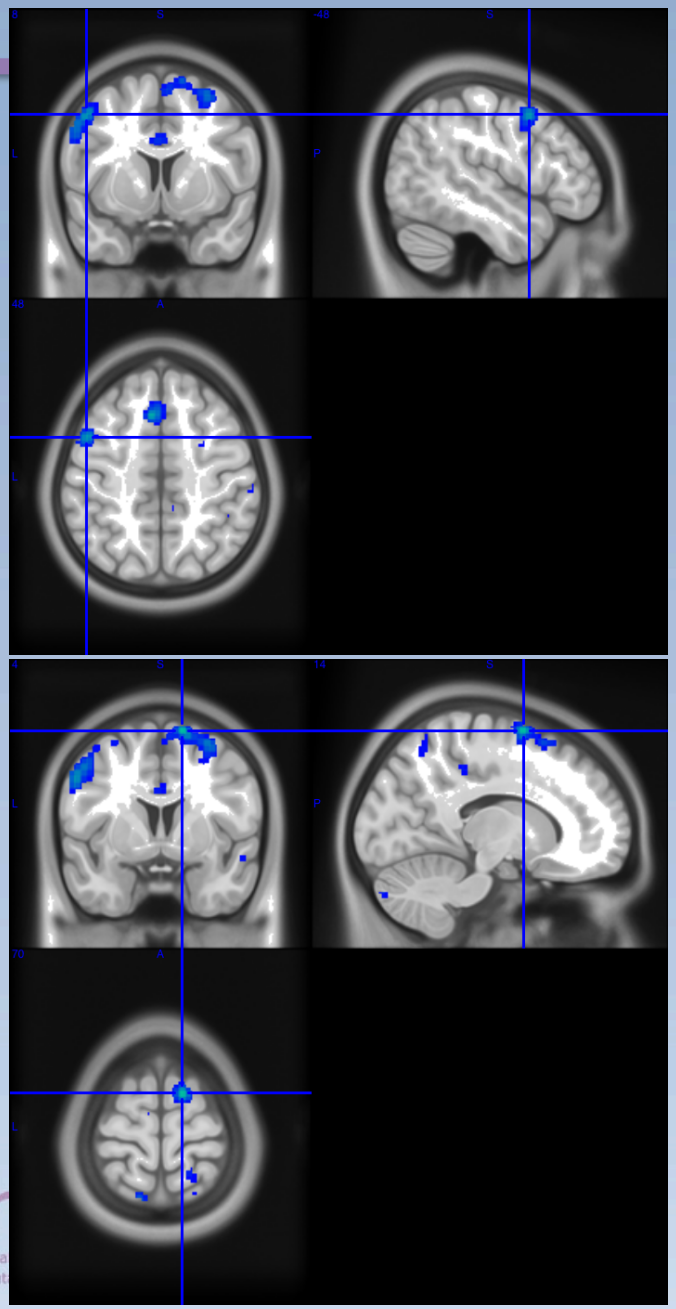
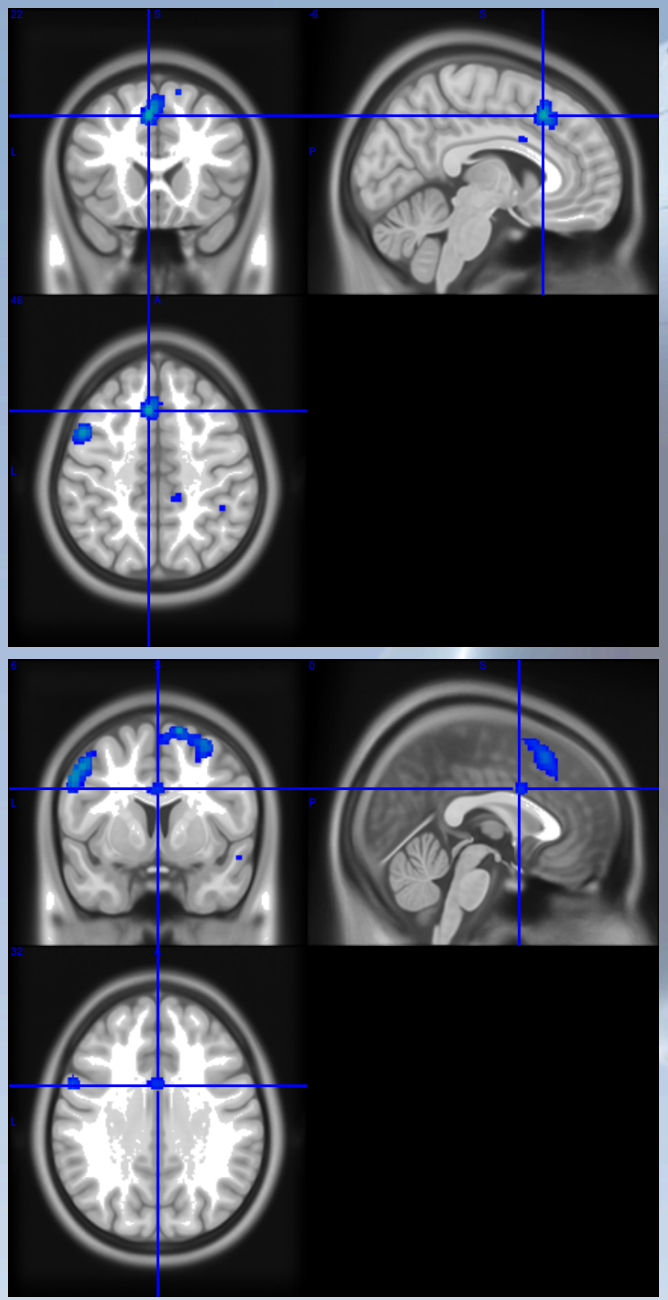
The Neurobiology of Effort Valuation in a Virtual Environment





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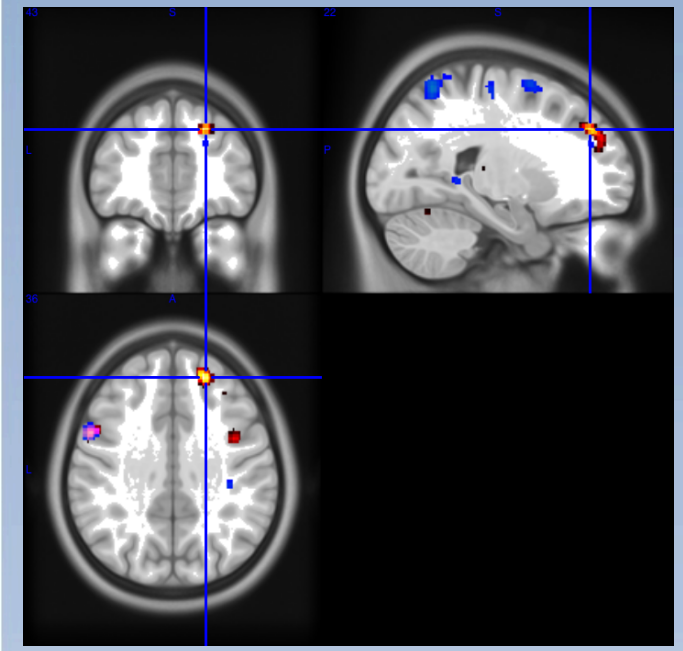
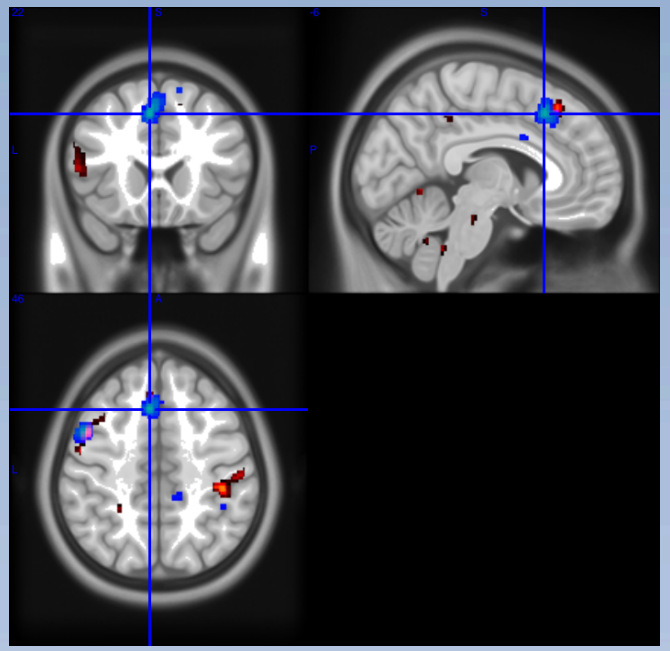
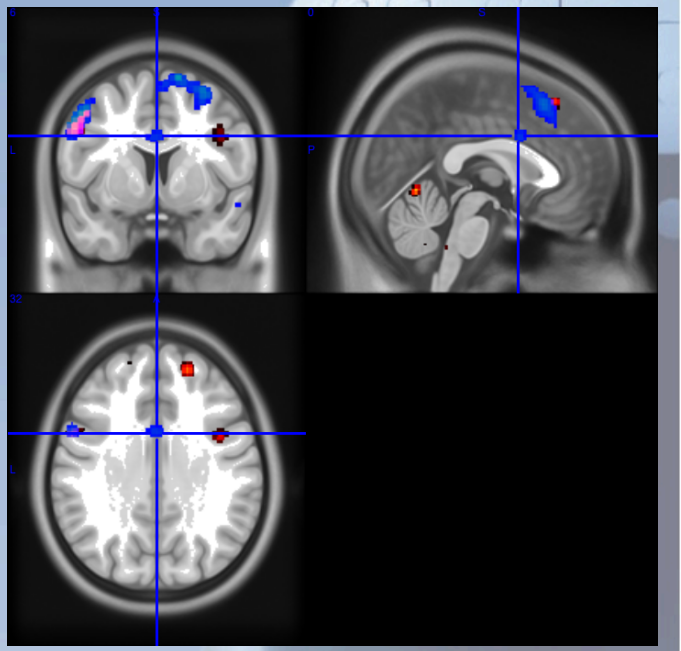
The Neurobiology of Effort Valuation in a Virtual Environment







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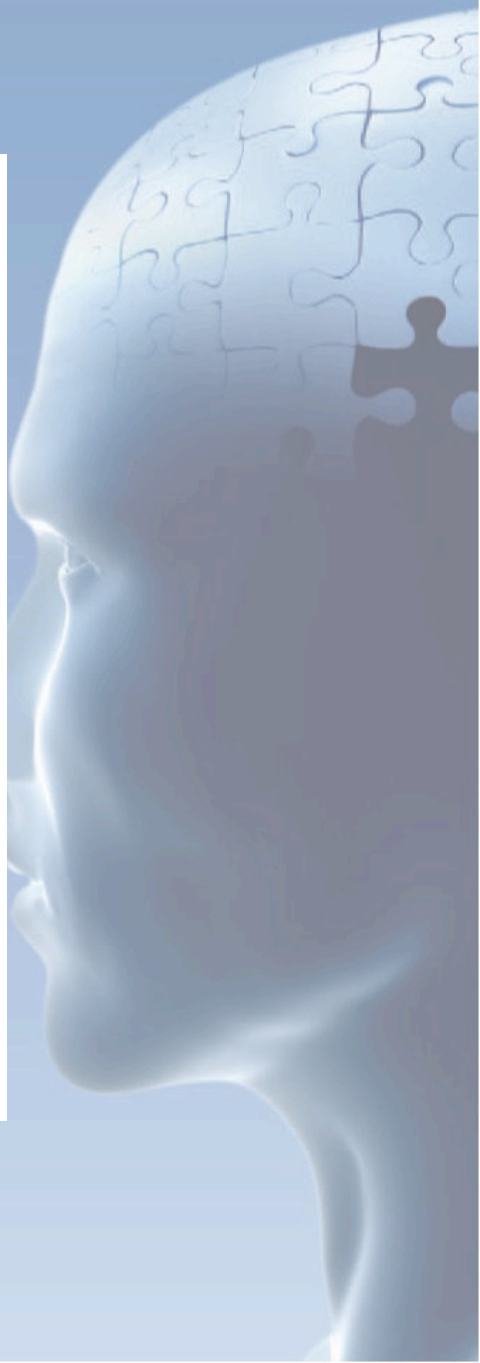
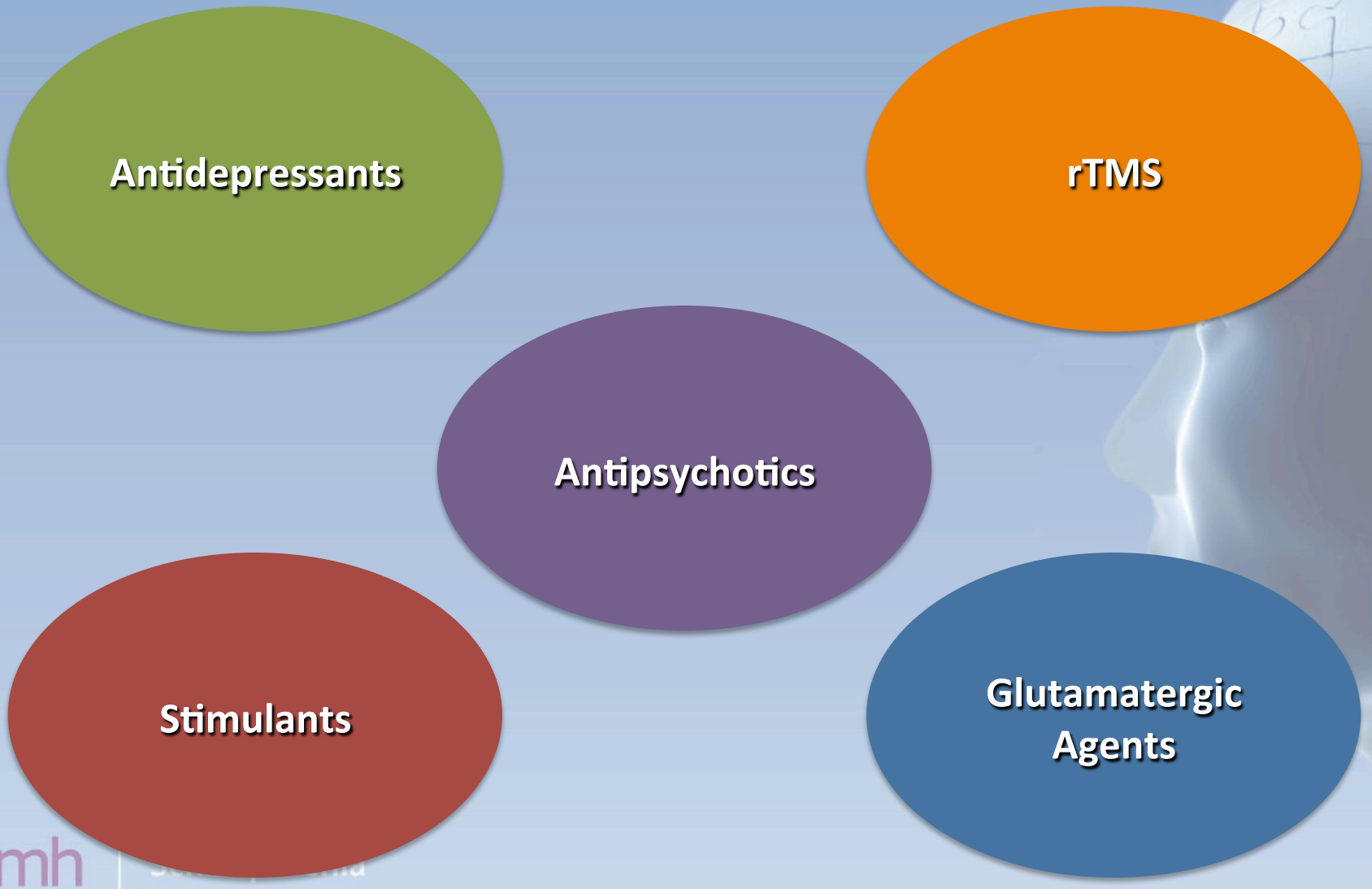
Schizophrenia
Research

Novel Strategies for Treating Motivational Deficits?

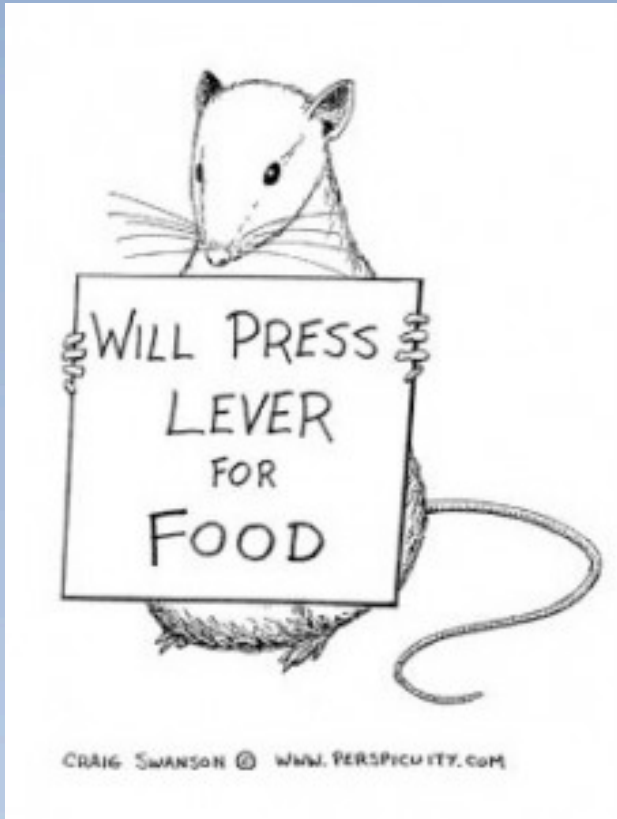


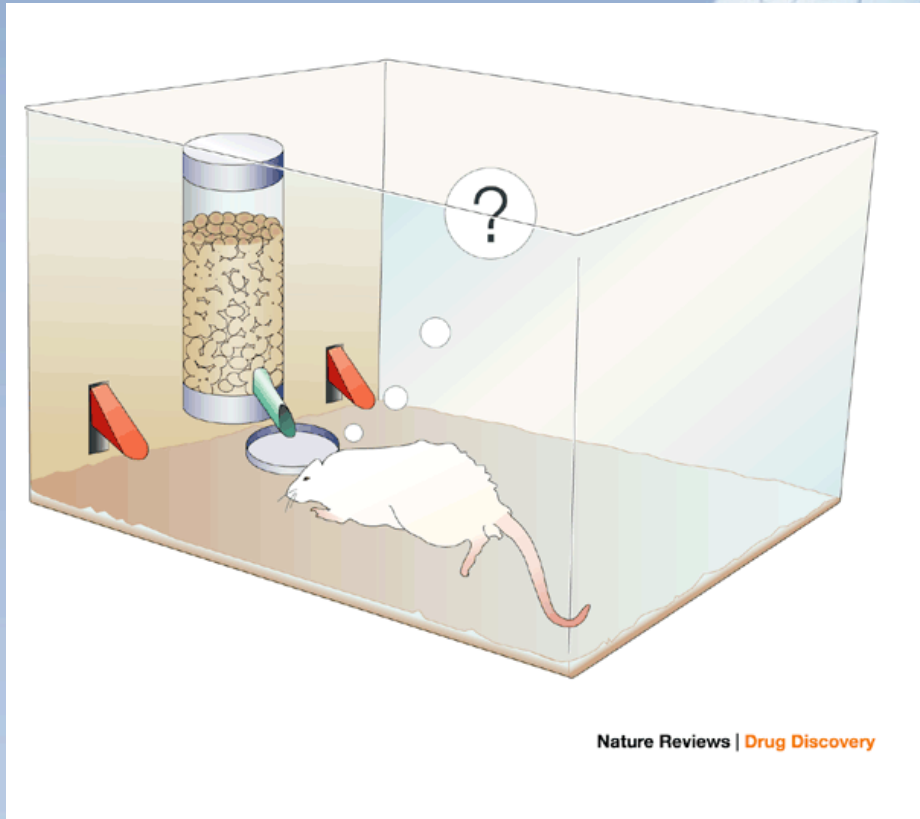
Treatments for Negative Symptoms in Schizophrenia



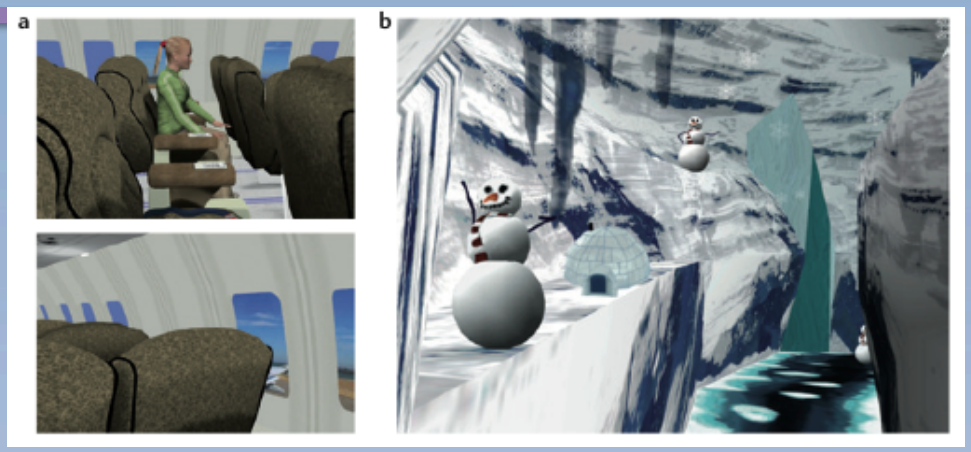
Rummel et al. 2006; Murphy et al. 2006; Tuominen et al. 2006; Buckley et al. 2007; Singh et al. 2010; Dlabac-de Lang et al. 2010 & 2014; Shi et al. 2014.

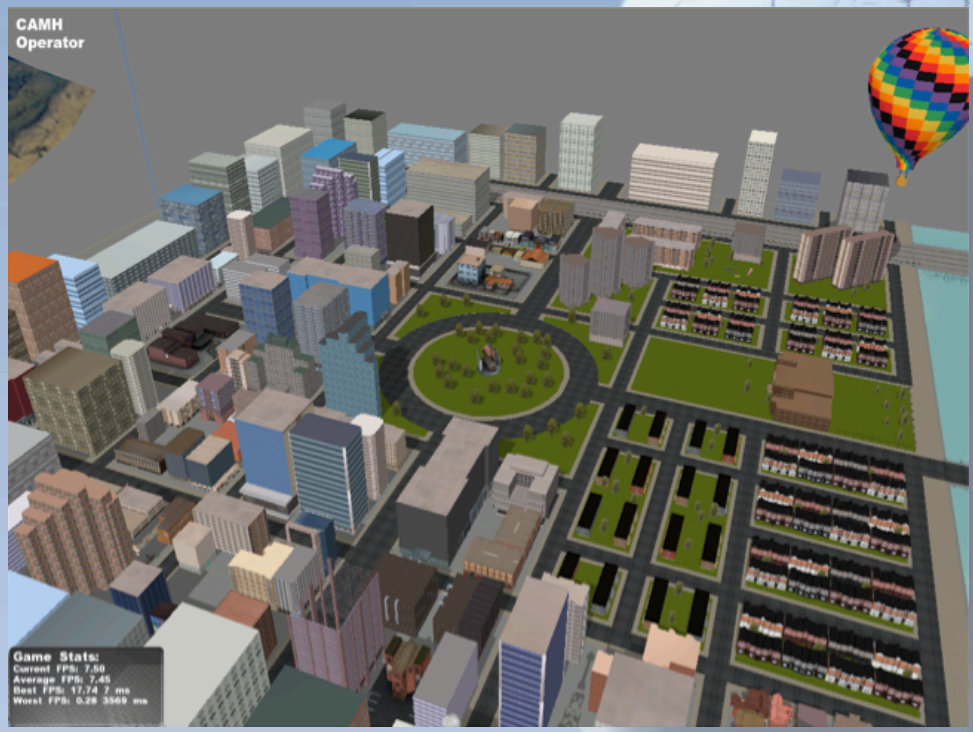
Novel Strategies for Treating Motivational Deficits?



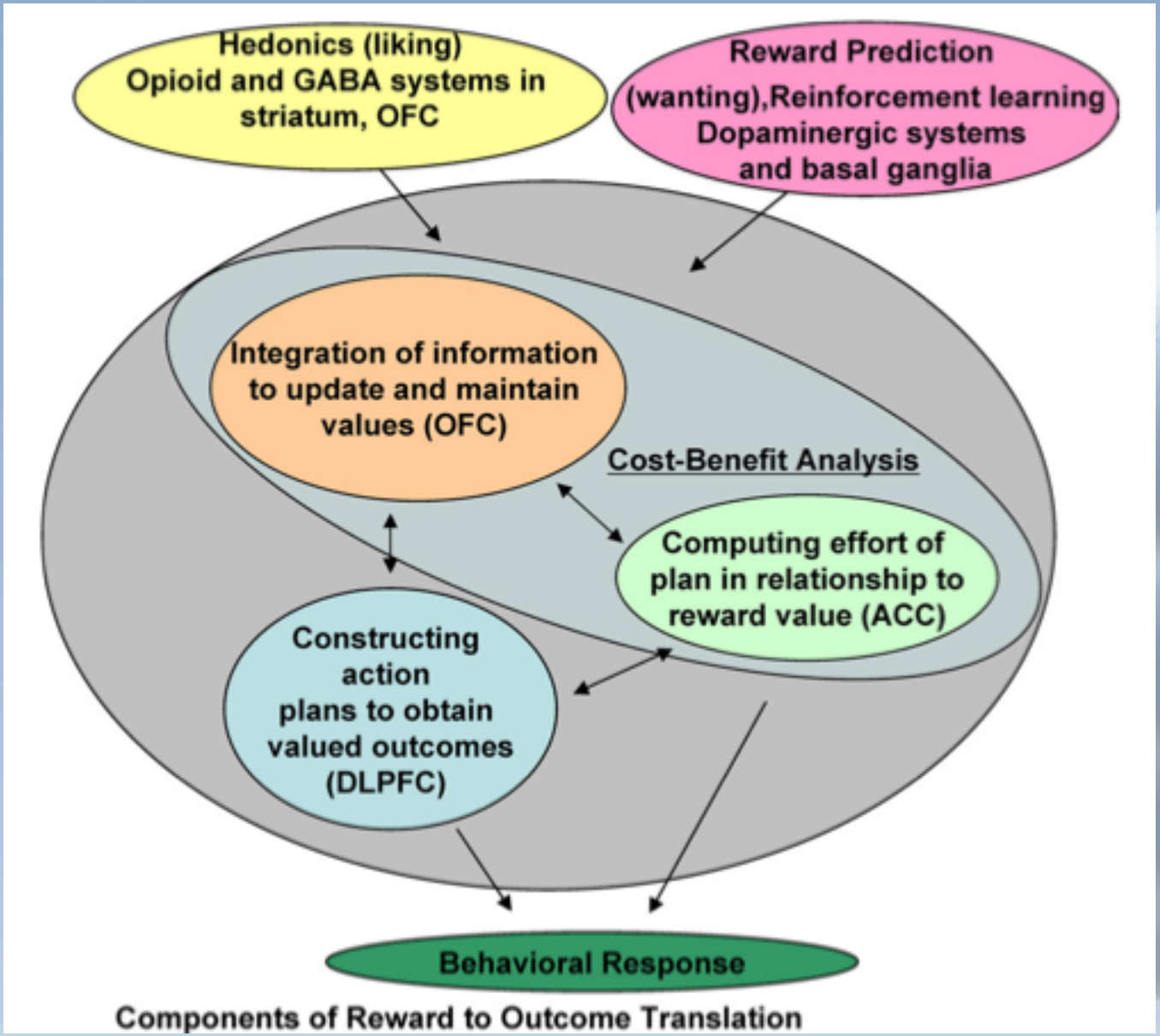


Virtual Reality Therapy





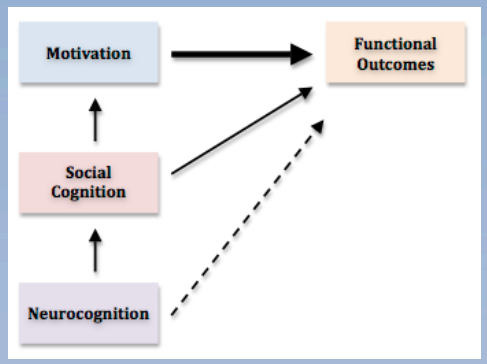
KNOCKED BUT YOU WEREN'T iN - OPPORTUNiTY

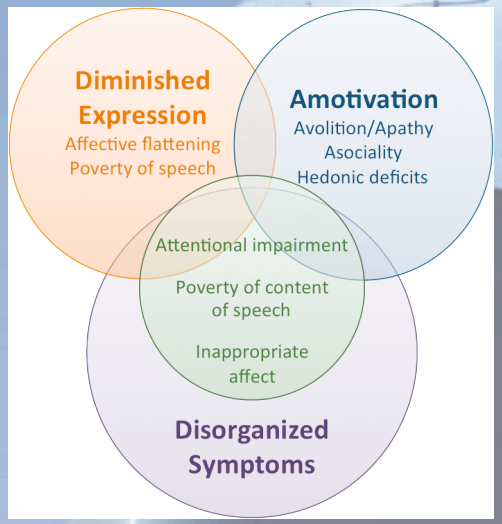


Components of Reward to Outcome Translation

Conclusions

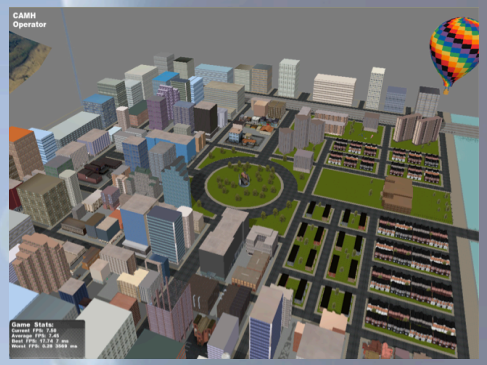
- Motivational deficits
  - The critical link between negative symptoms and functional outcomes
  - Indirect role through cognitive function
  - Impact on cognitive test performance





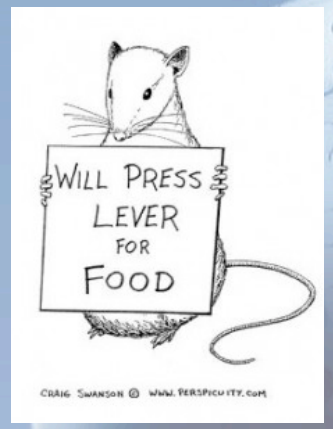
Conclusions

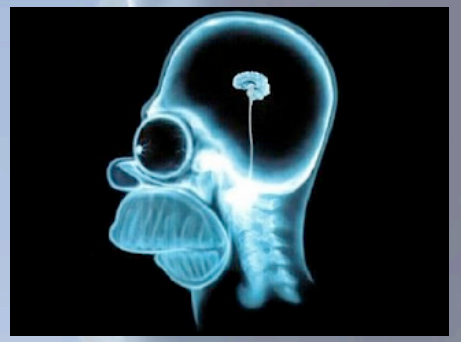
- Hedonic capacity is intact in schizophrenia
- Deficits:
  - Reward prediction / "wanting"
  - Reward and Effort valuation
    - Cost-benefit analysis
  - Goal-directed planning and action
- Patient-specific deficits?



Conclusions

- Novel treatment strategies for motivational deficits in schizophrenia
  - Pharmacotherapy & Opportunity
  - Improved neurobiological understanding of specific deficits
  - VR rehabilitation?
  - Personalized treatment for specific deficits





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Société Ontarienne de la Schizophrénie
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