THE ROLE OF DORSAL ANTERIOR CINGULATE CORTEX IN MOTOR CONTROL

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Acknowledgment

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More specifically, I would like to thank five groups of people, without whom this defense would not have been possible:

- I would like to start with the person who made the biggest difference in my life, my mentor, **Dr.Steven Bressler**, who taught me many skills that will be beneficial to me in my future career. His guidance and supervision showed me how to be a critical thinker, articulate a vision, focus a debate, and cut to the essence of an argument, making a point compelling, even to those who disagree.

- I also would like to thank my Co-advisor **Dr. Vaibhav A. Diwadkar** for his leadership, expertise and his talent. Thank You!

- A good support system is important to surviving and staying sane in grad school. I was lucky, I would like to express my gratitude to the members of my dissertation committee for taking the time to help me to prepare for this defense. I also want to thank them for their brilliant comments and suggestions, thanks to :

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Dr.Robert W. Stackman, Ph.D.

Dr.Ryne Sherman, Ph.D.

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- ❖ I also thank Ms. Keyla Thamsten for providing support and friendship that I needed.

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- ❖Last but not least, my **Mom** and my **Sister** unconditional love and encouragement have helped me persevere those many times that I was so devastated.

"God uses his people in ways one can not imagine."

Outline

1)Purpose of the Study
2)Anatomy and Function
3)Highlights from Other Literature
4)Research Question
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6)Results
7)Conclusions
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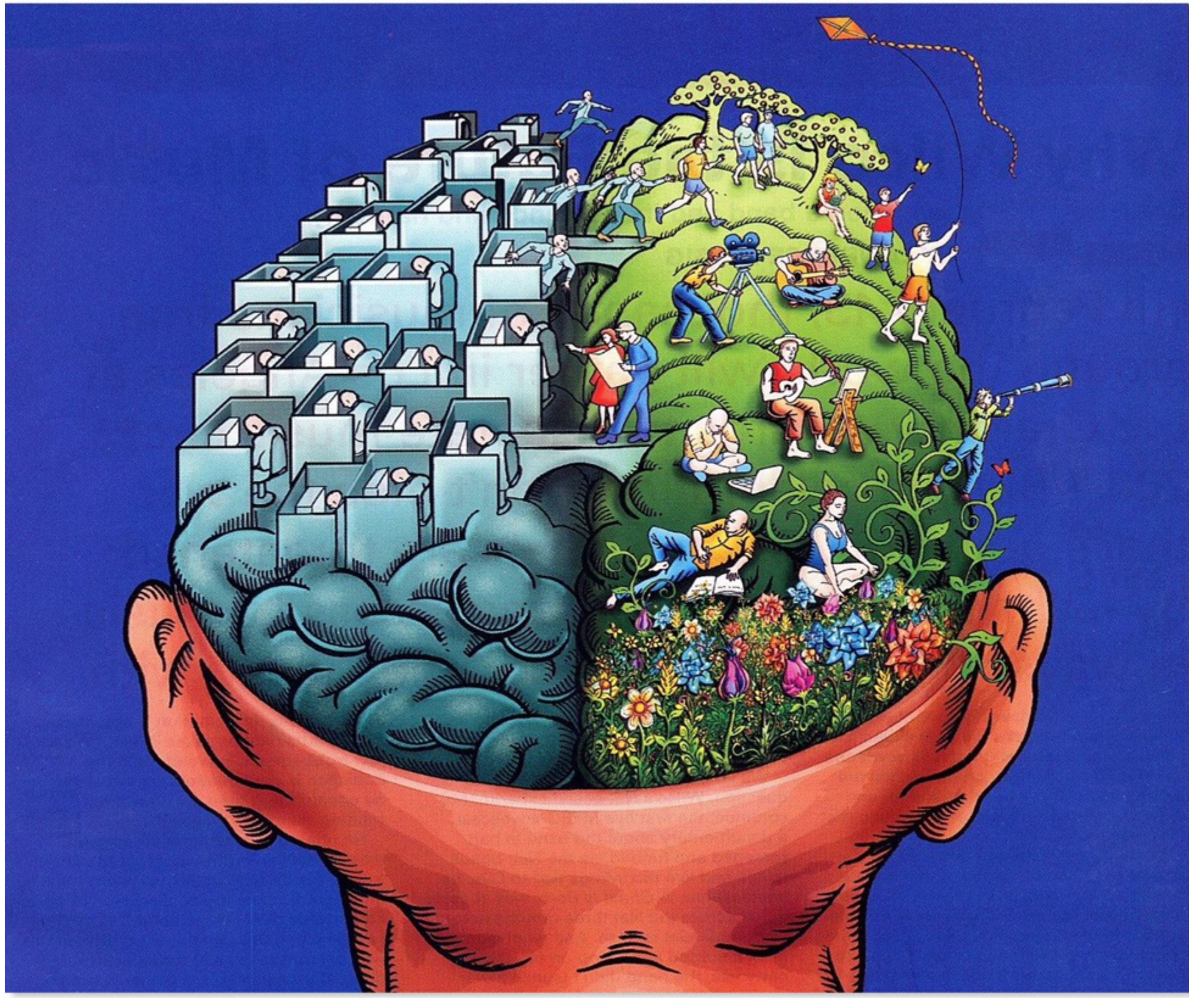


Purpose of the Study

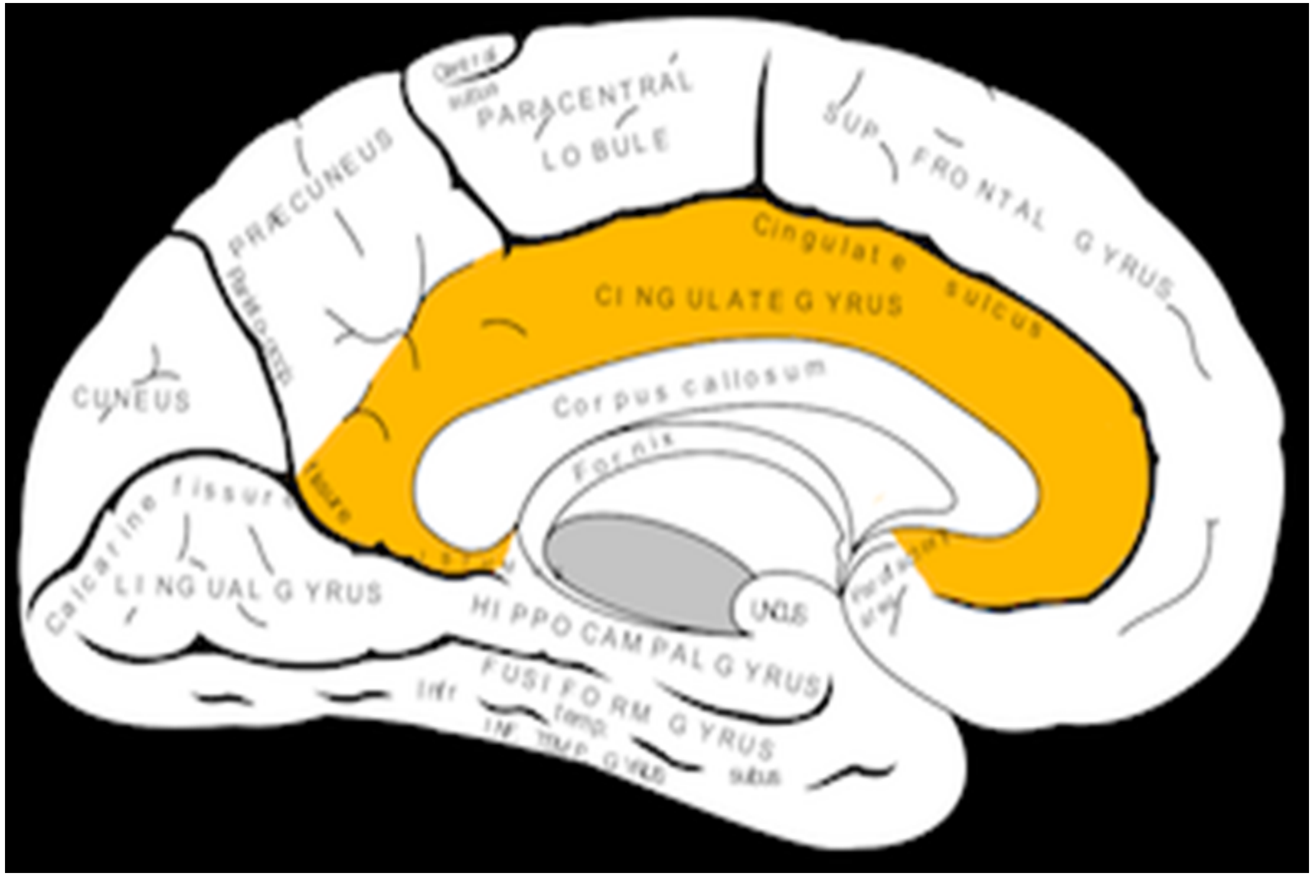
My study addresses the role of dorsal anterior cingulate cortex in motor control.

Anatomy and Function

Cingulate Cortex

- **The cingulate cortex resembles a "collar" surrounding the corpus callosum.**

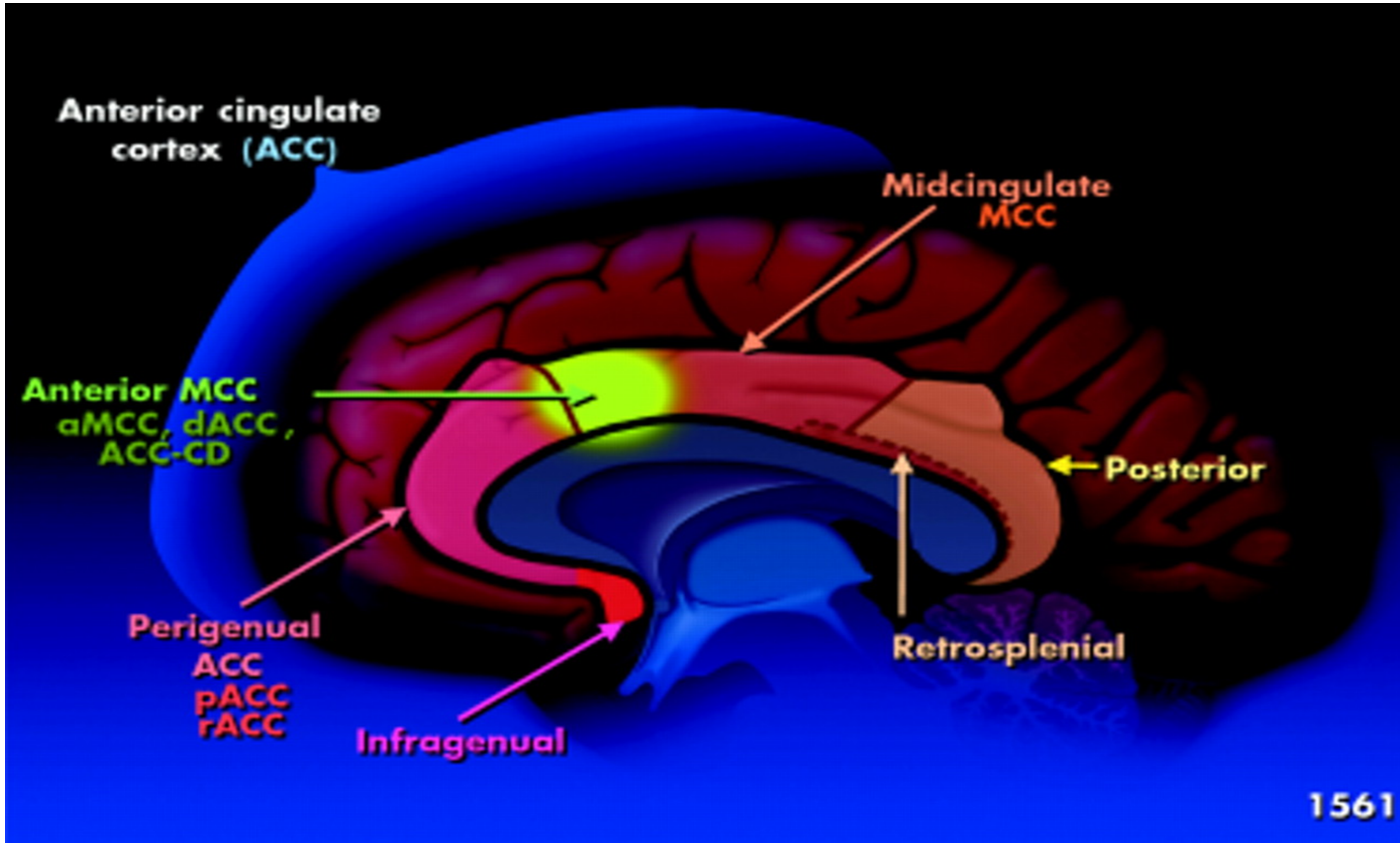
- **Anterior cingulate cortex is situated in the medial frontal cortex.**



Dorsal Anterior Cingulate Cortex

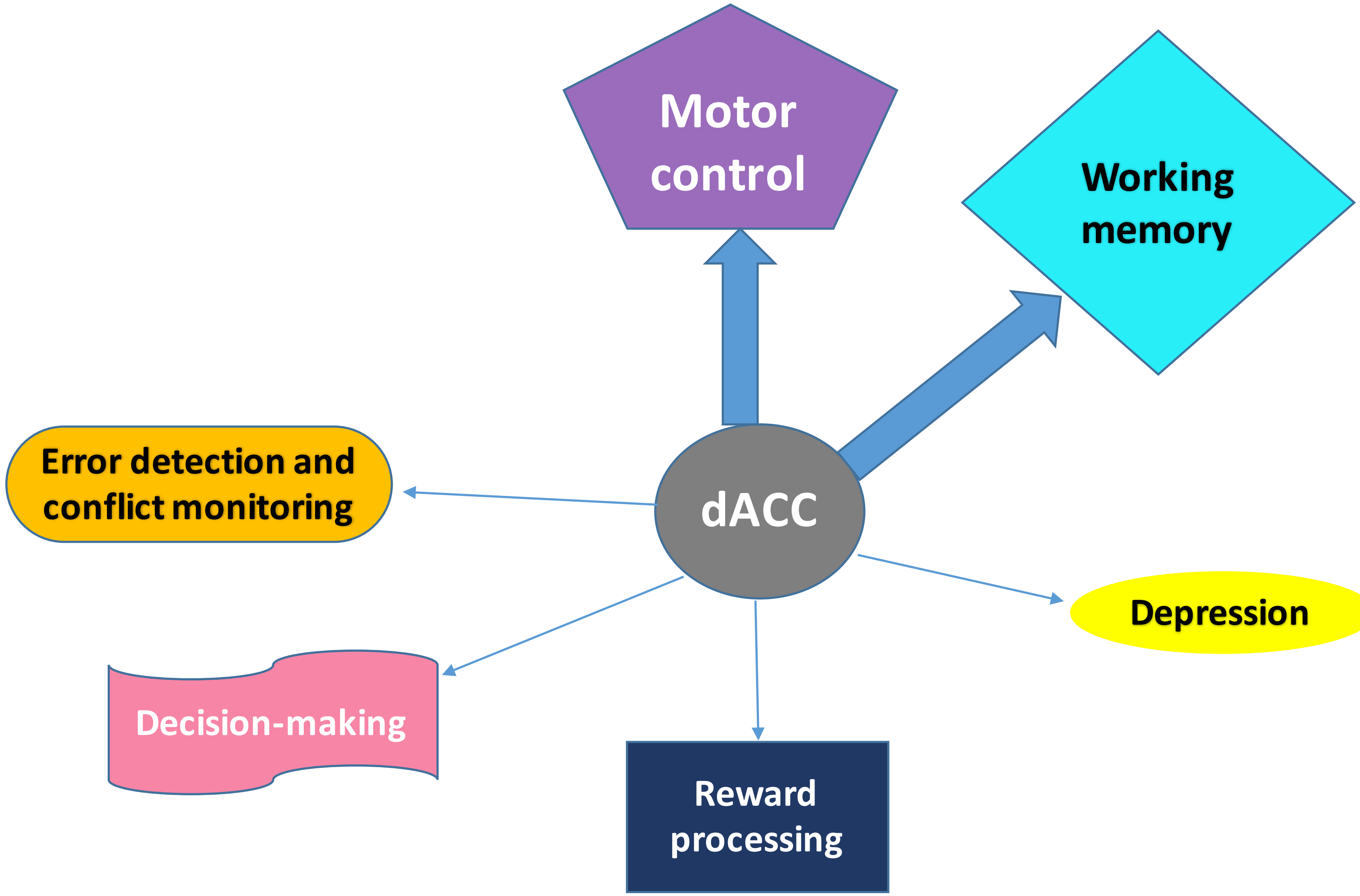
Anterior cingulate (ACC)

(d; dorsal, v;ventral, perigenual)



- ❖Dorsal ACC: Brodman areas 24 and 32. Has a role in Cognitive function.

Functional Heterogeneity in dACC :



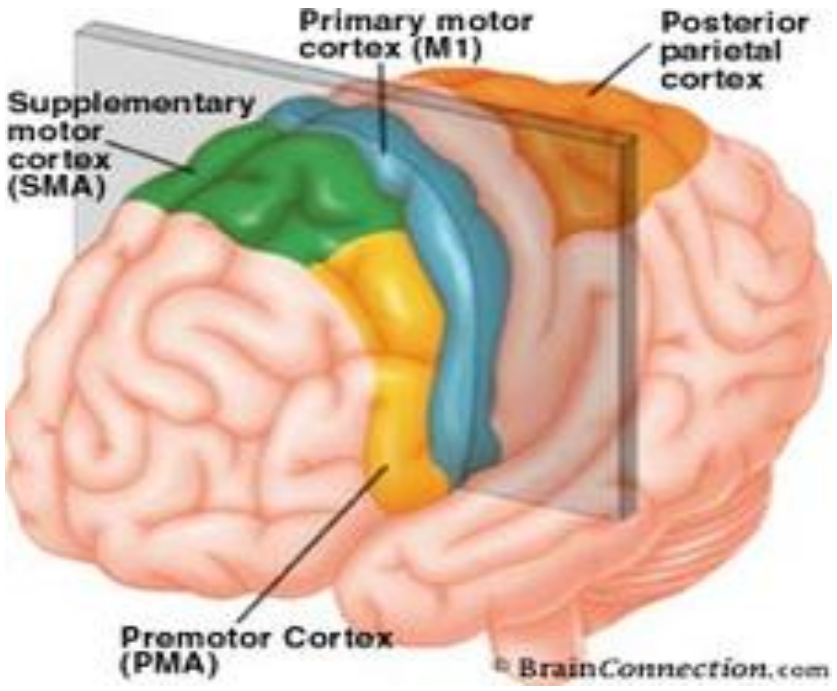
To study the role of dACC in motor function we looked at it's relation with two other parts of motor cortex:

- Primary Motor Cortex (BA4).

a) Contralateral to right index finger region of M1.

- Medial premotor cortex also called 6b or Supplementary Motor Area (SMA).

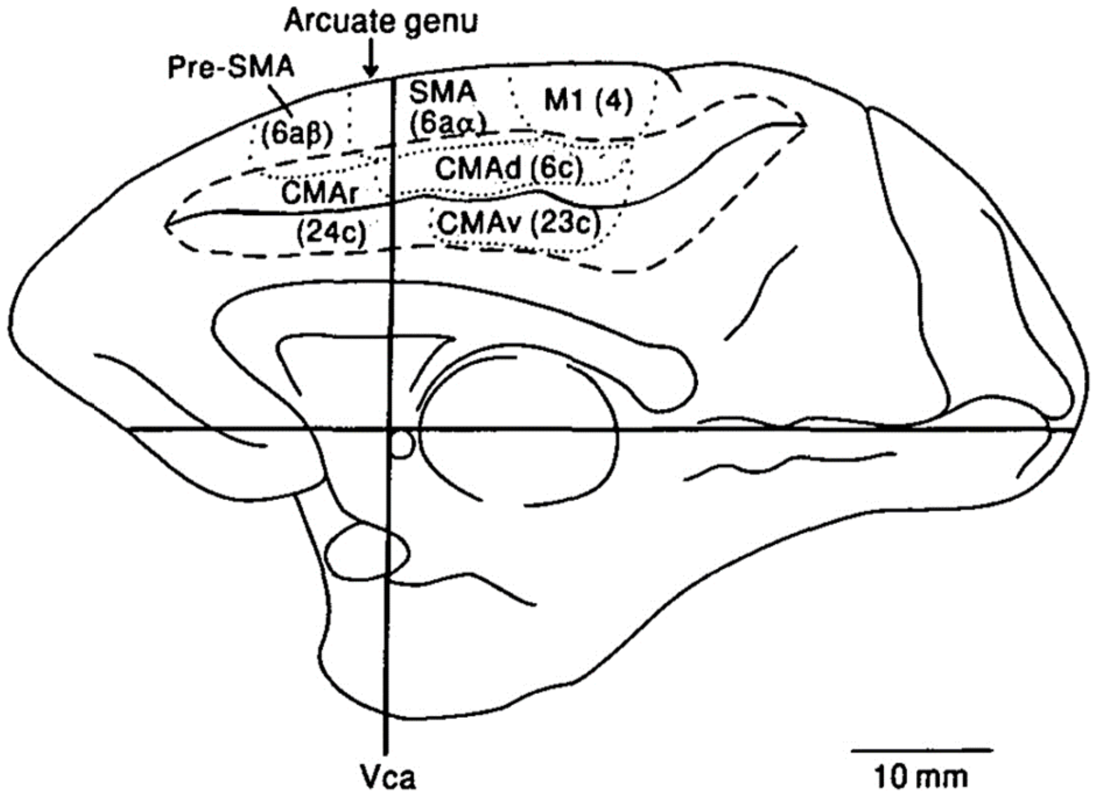
a) SMA is hierarchically higher than M1.



Highlights from Other Literature

SMA in Humans is Analogous to Monkey 6aa and 6ab

In the macaque monkey, a caudal (posterior) area 6aa and a rostral (anterior) area 6ab on the medial surface of the brain correspond reasonably well to the human SMA, respectively (Matelli etal.,1991, Tanji et al., 1994).



Perpendicular line crossing the anterior commissure (Vca)

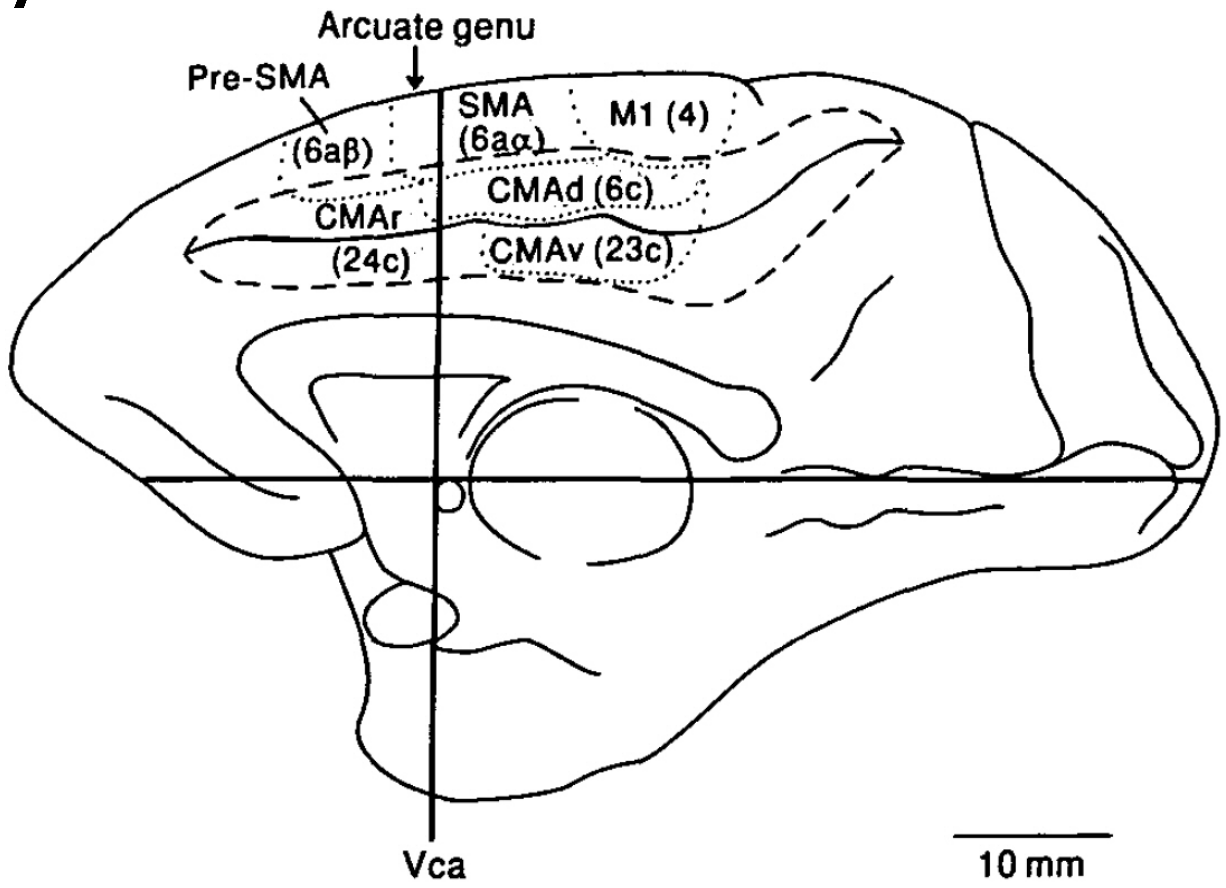
The intersection of the bicommissural line (CA-CP)

Location of motor areas in the medial wall of the hemispheres of the monkey

- Picard, N., & Strick (1996) have tentatively associated the dACC of humans with the CMAr of monkeys.

- There is substantial evidence that dACC is anatomically connected to the motor system:

❖Evidence from anatomical pathway tracing suggests that the dACC projects directly to the SMA in monkeys (Luppino et al. 1990; Matelli et al. 1991; Morecraft & Van Hoesen 1992).



Functional Evidence for Involvement of dACC in Motor Control

I. There is clinical evidence that dACC is functionally involved in motor control (Devinsky et al., 1995; Mesulam, 1981; Fellows, 2005; Milham & Banich, 2005).

II. Electrical stimulation in animals has also been used to demonstrate a motor role for dACC (Luppino et al., 1991; Picard & Strick, 2001).

III. Neuroimaging studies have confirmed that motor regions of the human dACC are activated during manual movement (Paus et al., 1993, 1998).

Functional Connectivity of dACC in Motor Control

The role of the dACC in motor control is under-characterized.

The quantitative analysis of connectivity requires sophisticated mathematical and statistical techniques.

Previous studies using resting-state undirected functional connectivity analysis have shown:

- The anterior midcingulate cortex is involved in motor control (Hoffstaedter et al., 2013).
- The dACC is involved in selecting and preparing the appropriate behavioral responses to achieve higher-level goals (Shulz et al., 2011).

What Is Missing from the Field?

- A wide gap currently exists between our understanding of neurocognitive network structure, function, and dynamics and a deeper understanding of human behavior.
- To better understand human behavior, a network approach to brain function is needed.
- We computed both directed and undirected functional connectivity between the dACC and SMA to investigate the role of the dACC in motor control.

What is a Brain Network?

- A brain network is a biological realization of a mathematical entity called a graph.
- A network consists of nodes connected by edges.
- In our study, an individual voxel standing for a brain region represents a node.
- These projects seek to identify and quantify functional network edges through the use of functional connectivity analysis.

What is Functional Connectivity (FC)?

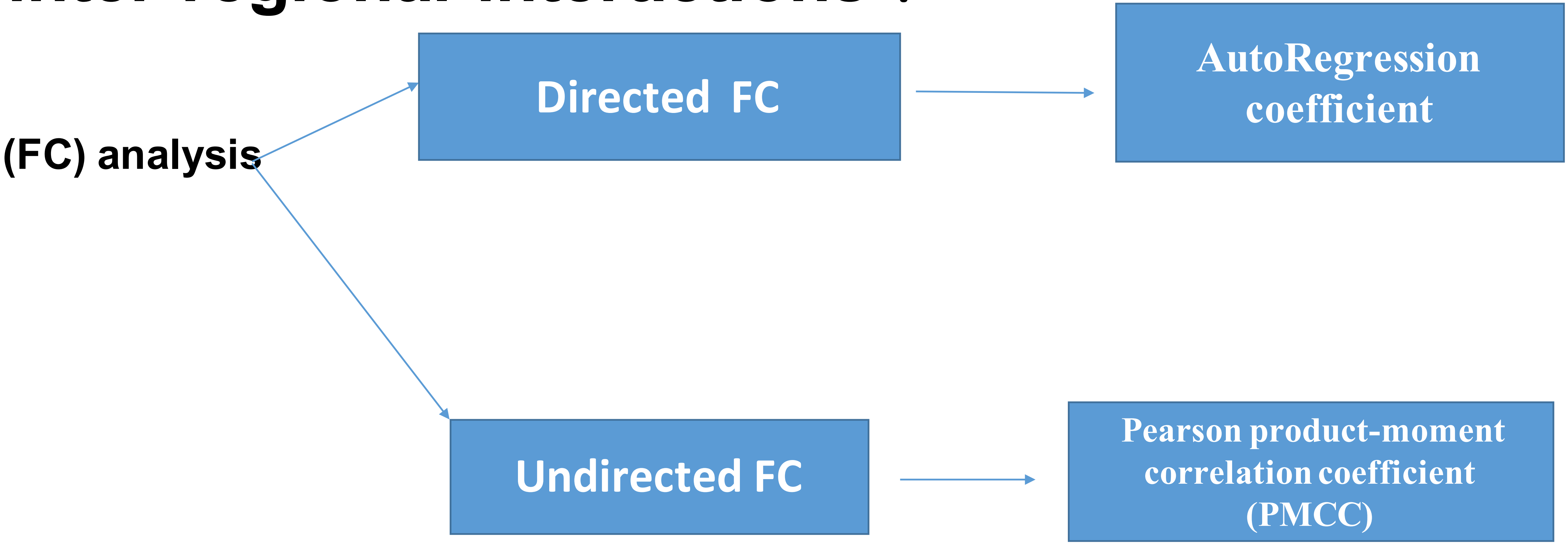
- Statistical dependencies (correlation or regression between nodal activities) are derived from time series.
- The time series come from the variety of types of neural data including EEG,MEG, ECoG and blood oxygenation level–dependent (BOLD) functional MRI (fMRI).
- Able to measure the spatial path that information follows from one region to another region.

Research Question

What is the role of dACC in motor control?

❖ What is the functional relation of the dACC with/to the SMA and M1using both undirected and directed functional connectivity?

Measuring functional connectivity: We used established methods for characterizing inter-regional interactions :



Asemi et al., 2015

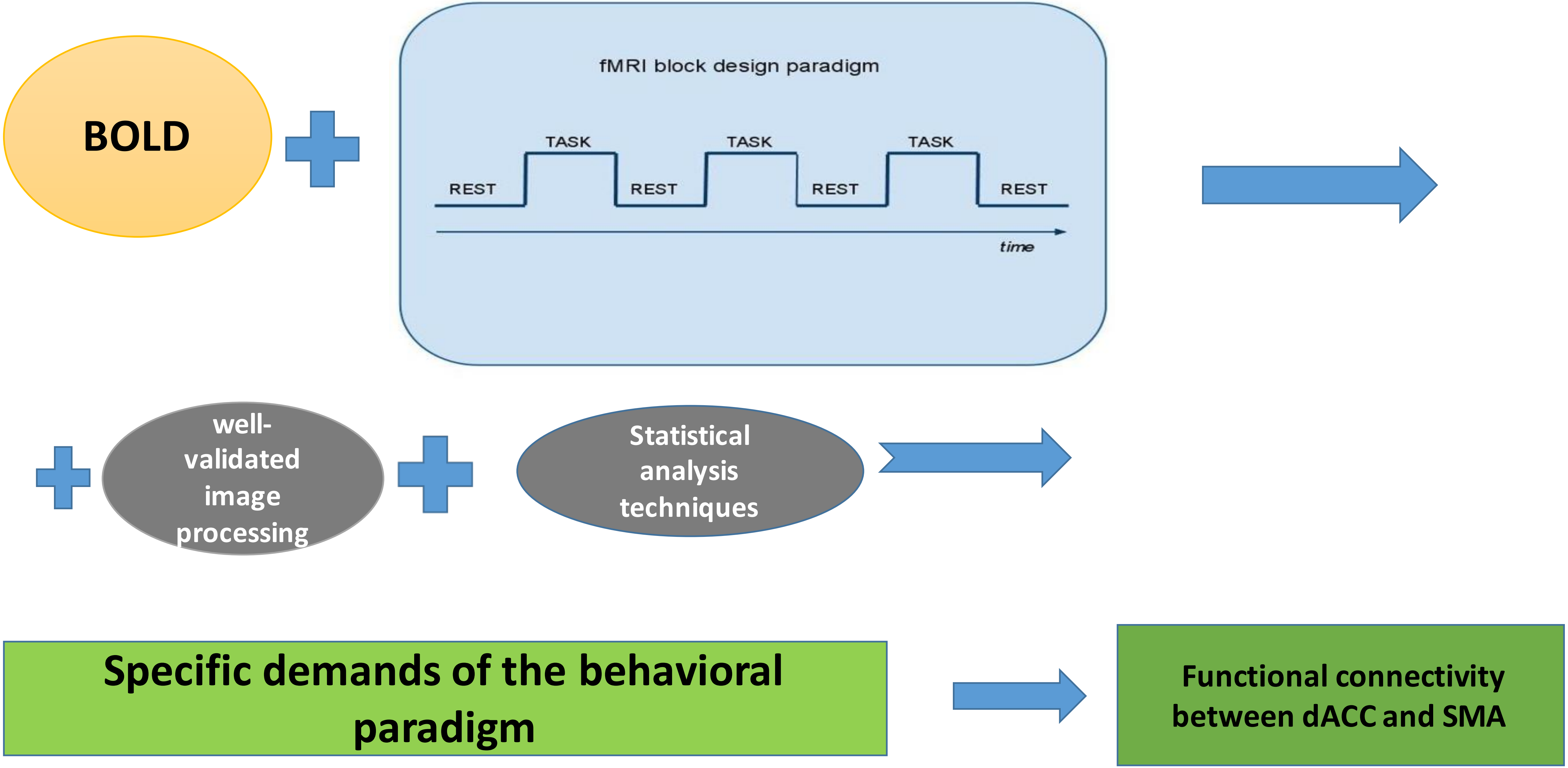
Functional Connectivity

- The strength of undirected functional connectivity of one ROI with another was estimated by the magnitude of the PMCC computed using the cor function in the R software environment.

- The strength of directed functional connectivity from one ROI to another was estimated by the magnitude of a t-statistic from significance testing of the corresponding AR model coefficient computed in the GLM function in the R software environment.

a) This strength thus served as a metric for the dynamic causal relationship between the time series, and is similar to Granger causality in being derived from the MVAR model.

Methods and Materials

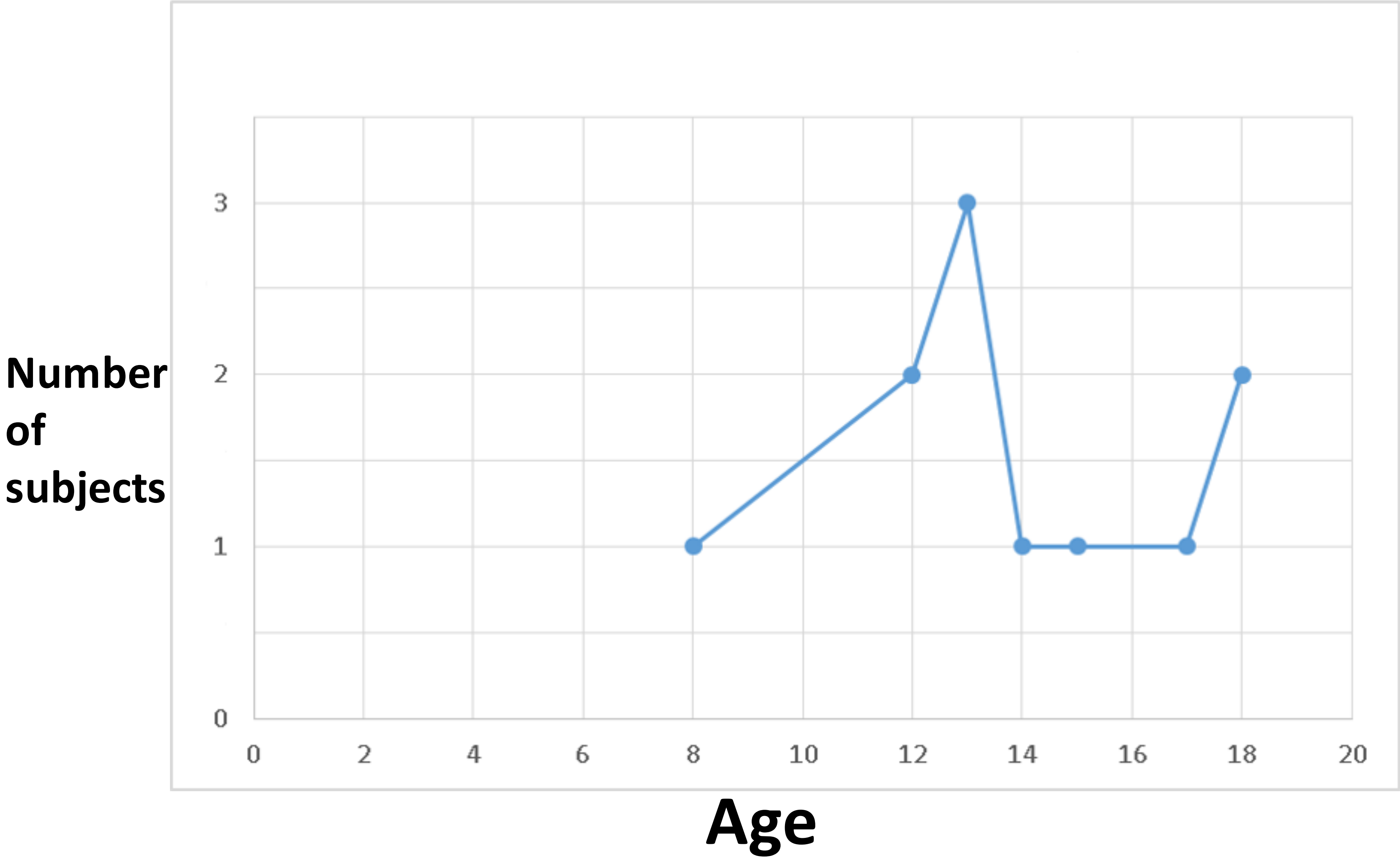

BOLD
fMRI block design paradigm
TASK
TASK
TASK
REST
REST
REST
REST
time
well-validated image processing
Statistical analysis techniques
Specific demands of the behavioral paradigm
Functional connectivity between dACC and SMA

Subjects in two Projects

- The subjects for both projects come from the same group of adolescents.

- In project one: 11 Healthy adolescent participants
- In project two: 10 Healthy adolescent participants

Age of participants in both tasks: Coordinated motor task and nb-task



4) Methods and Materials

Project 1

Behavioral Paradigms

Projects

1

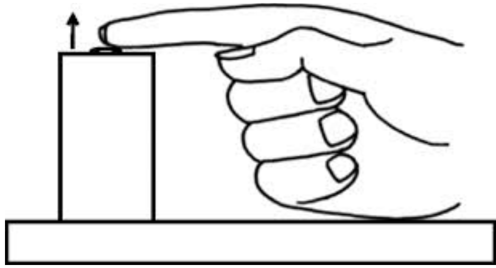
Coordinated unimanual finger-movement in response to exogenous visual stimuli.

Tapping-Coordination (TP task)

vs

Rest

Control



2

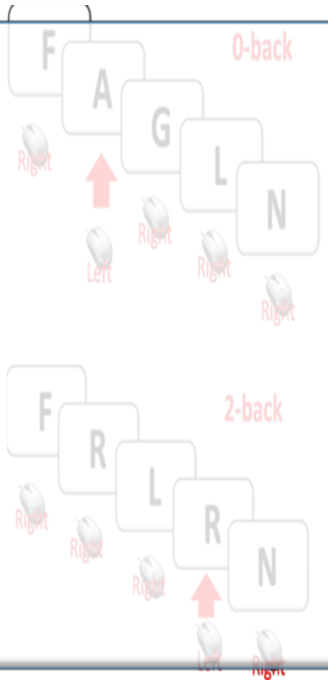
Coordinated unimanual finger-movement in response to exogenous visual stimuli.

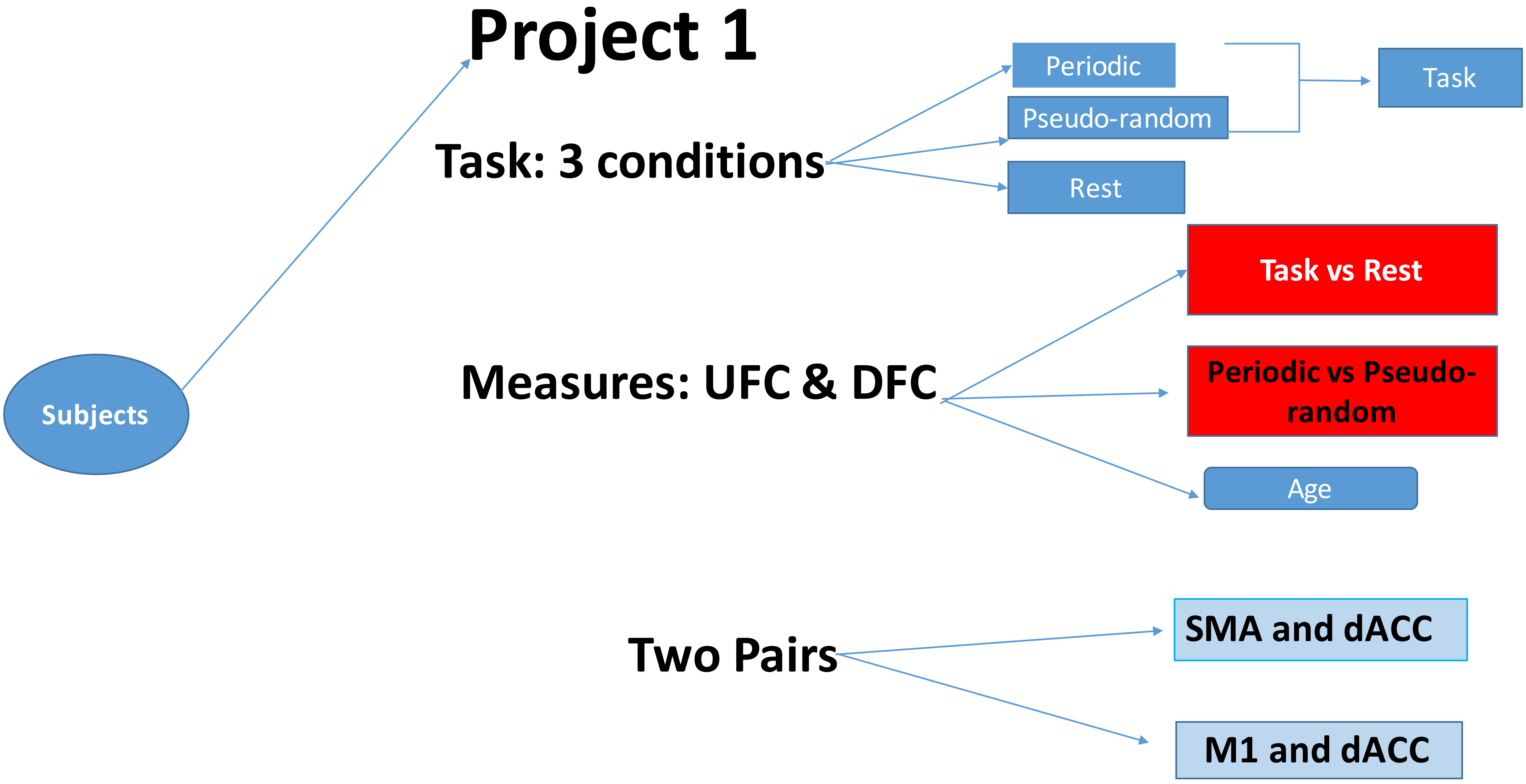
Tapping-Coordination (TP task)

vs

n-back working memory

Control




Project 1
Subjects
Task: 3 conditions
Periodic
Pseudo-random
Rest
Task
Measures: UFC & DFC
Task vs Rest
Periodic vs Pseudo-random
Age
Two Pairs
SMA and dACC
M1 and dACC

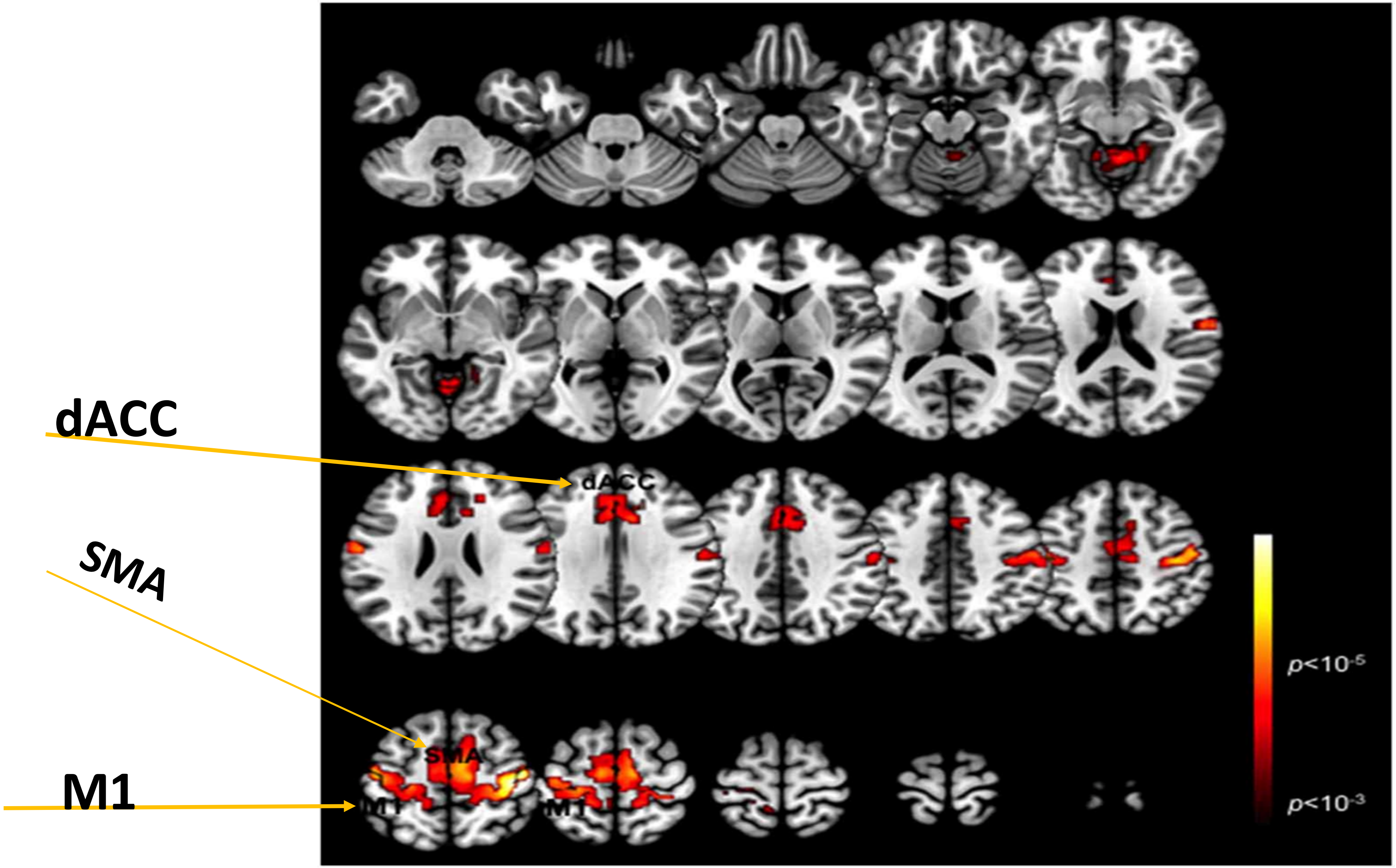
Results

a. Activation
b. UFC
c. DFC
d. AGE

Project 1

Activation Map

Task-related BOLD activation maps. Activation patterns are shown for the conjunction of the two task variants (periodic and pseudo-random) averaged across participants. Significant activation clusters ($p < 0.01$, cluster level) are overlaid on a mosaic of axial views.



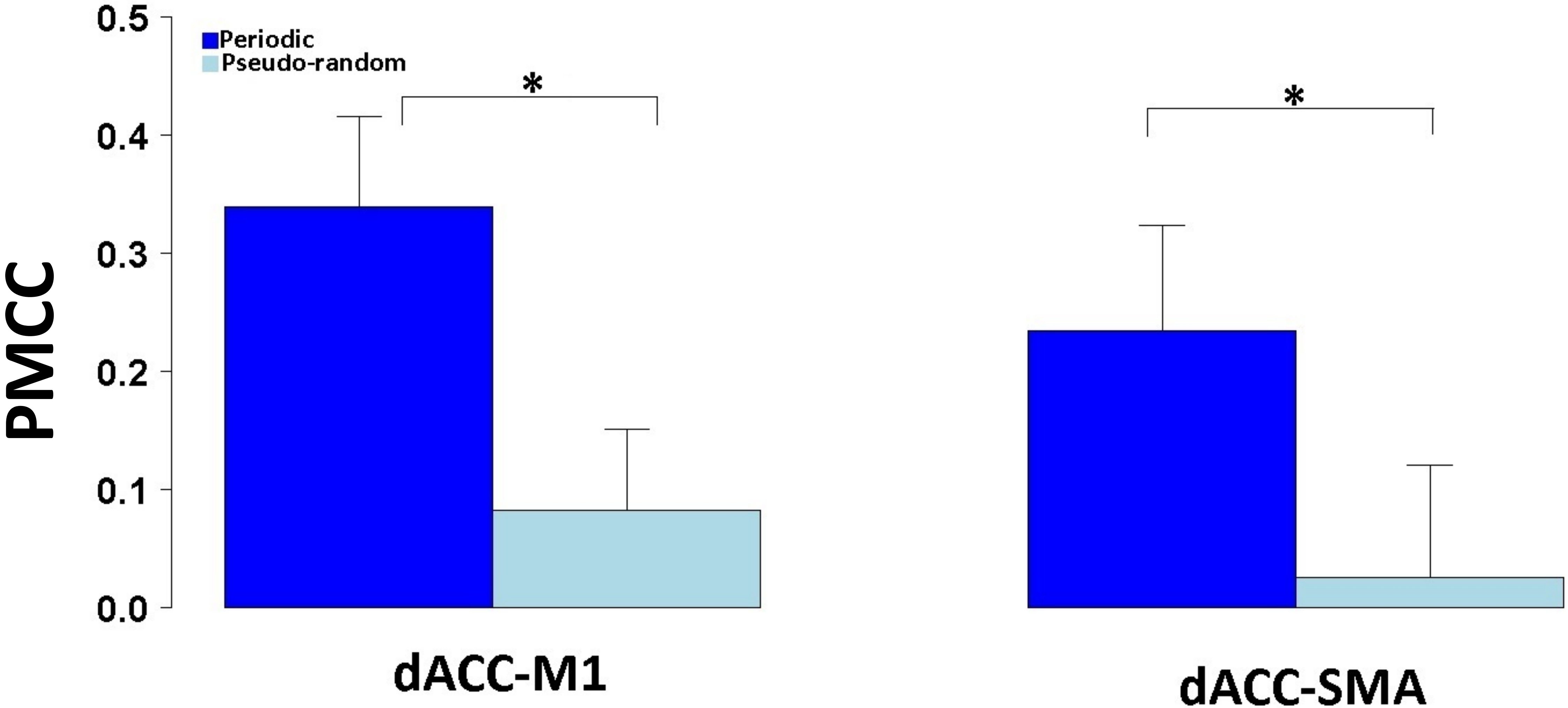
Undirected Functional Connectivity (UFC)

I. Task vs Rest
II. Periodic vs Pseudo-random

Undirected Functional Connectivity (UFC) Results

- Comparisons of **task vs. rest** conditions on the undirected functional connectivity (PMCC) between the **dACC** and the **SMA** were not significant by either the parametric paired t-test or the nonparametric Mann-Whitney-Wilcoxon signed-rank test.
- The same was true between the **dACC** and **M1**.

Undirected Functional connectivity (UFC):
By contrast, comparison of Periodic and Pseudo-random task conditions revealed that the correlations both between dACC and SMA, and between dACC and M1, were significantly greater in the Periodic than the Pseudo-random conditior

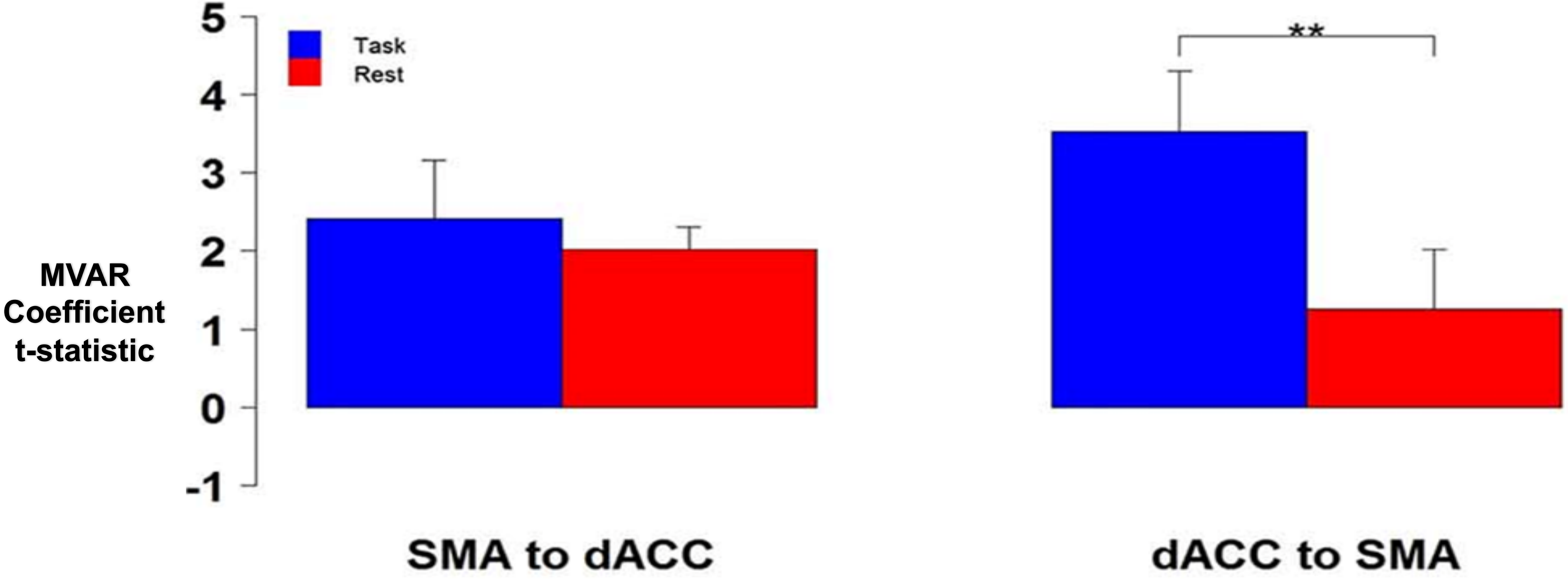


Directed Functional Connectivity

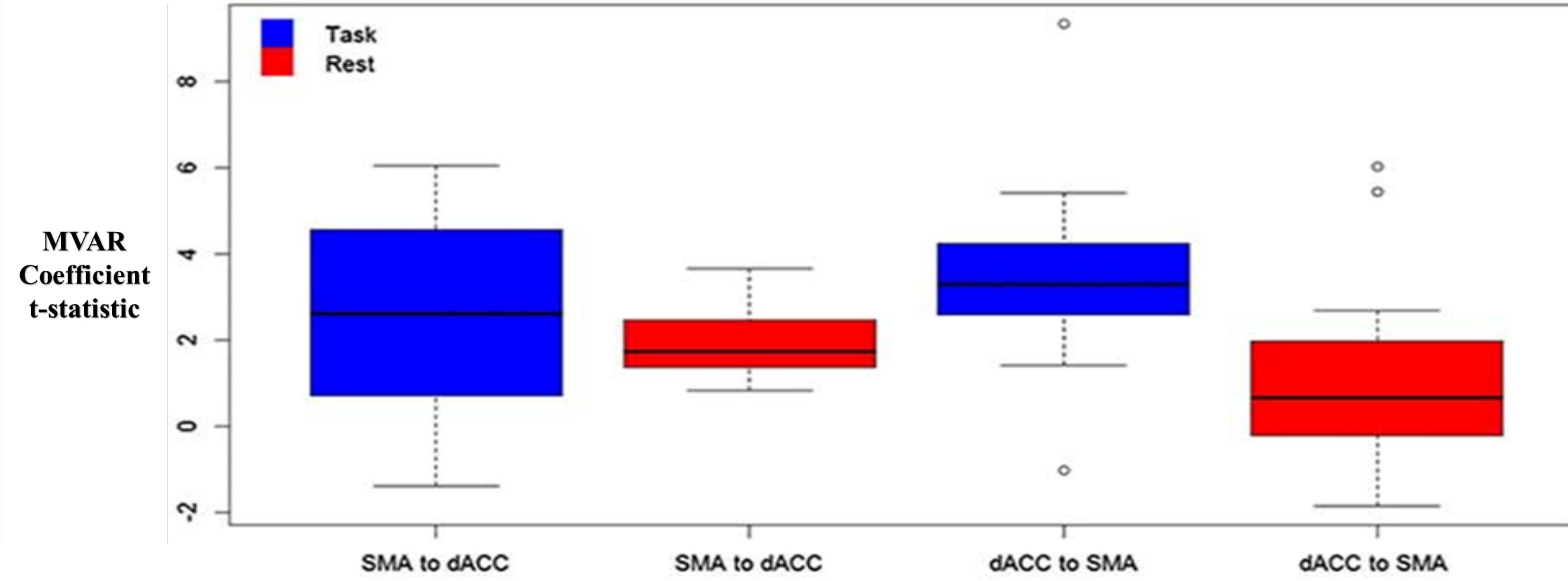
I. Task vs Rest
II. Periodic vs Psudo-random

Directed Functional Connectivity (DFC):

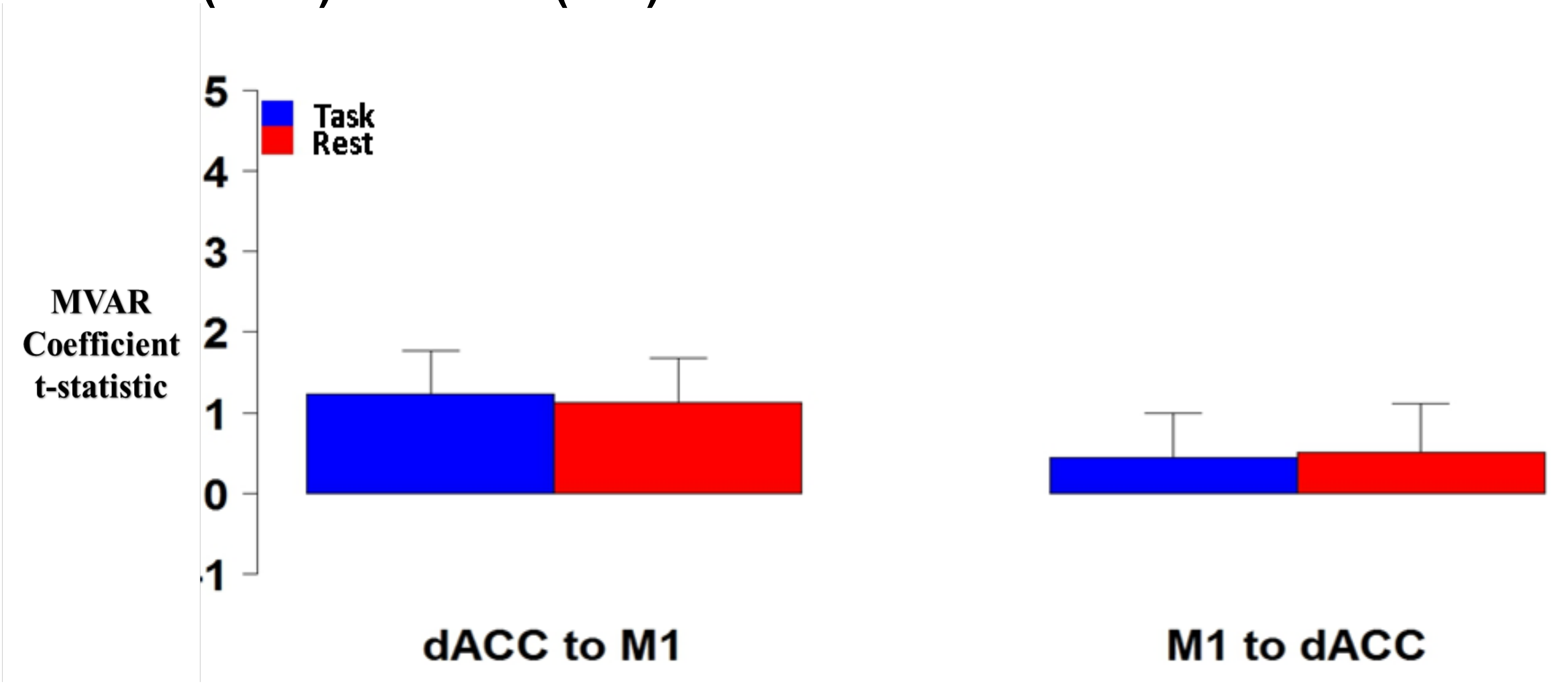
**The influence from dACC to SMA was significantly greater for task than rest, but the influence from SMA to dACC did not significantly differ
(**p < 0.01).**



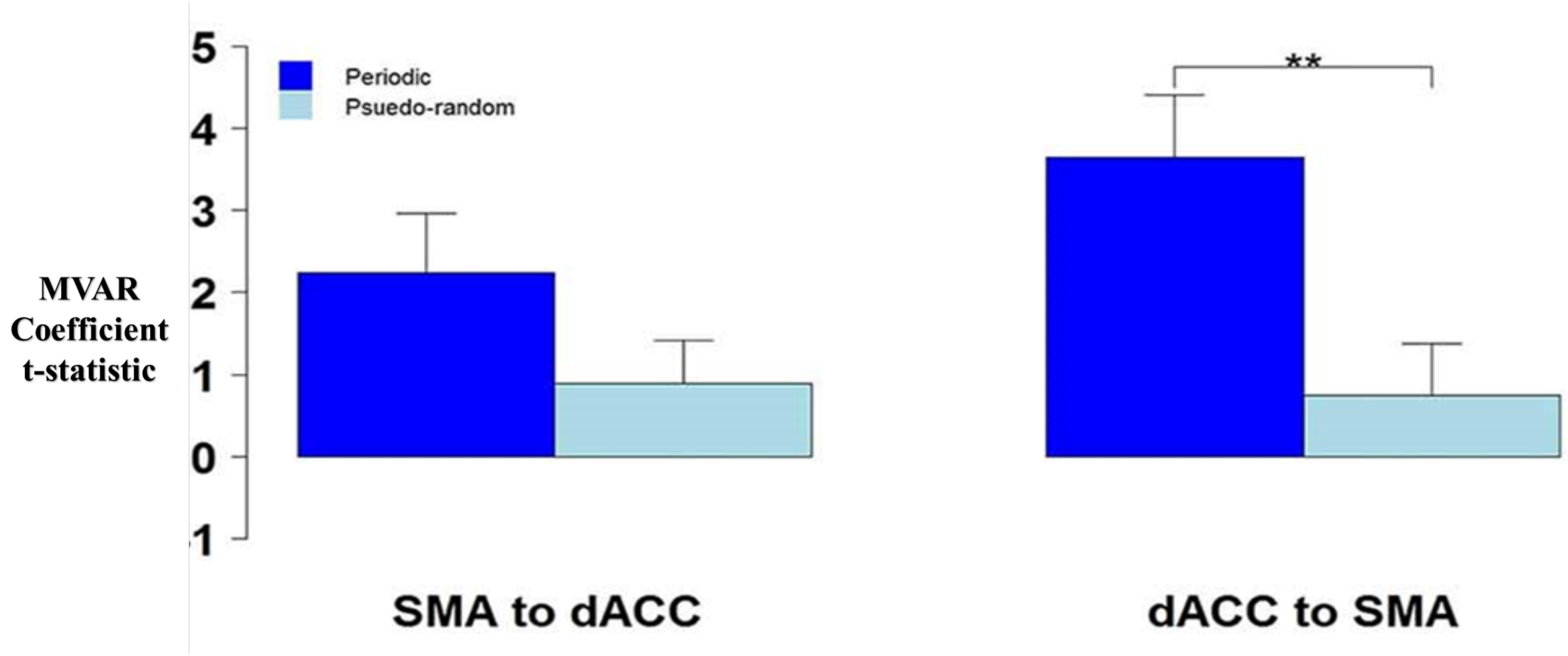
Directed Functional connectivity:
Note that the distribution for the influence from dACC to SMA during the task is both more compact than rest and elevated above the distribution during rest.



Directed Functional Connectivity:
The group mean and standard error of influence in both directions between the 2 ROIs (dACC to M1, M1 to dACC) for task (blue) and rest (red) conditions.



Directed Functional Connectivity:
The influence from dACC to SMA was significantly greater for periodic than pseudo-random conditions, but the influence from SMA to dACC did not significantly differ.($p < 0.01$).**



Age :

The task-specific modulatory influence from the dACC to the SMA was independent of age in all conditions.

Methods and Materials

Project 2

Behavioral Paradigms

Projects

1

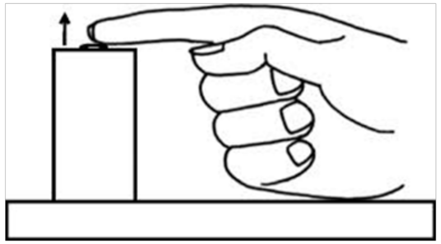
Coordinated unimanual finger-movement in response to exogenous visual stimuli.

Tapping-Coordination (TP task)

vs

Rest

Control



2

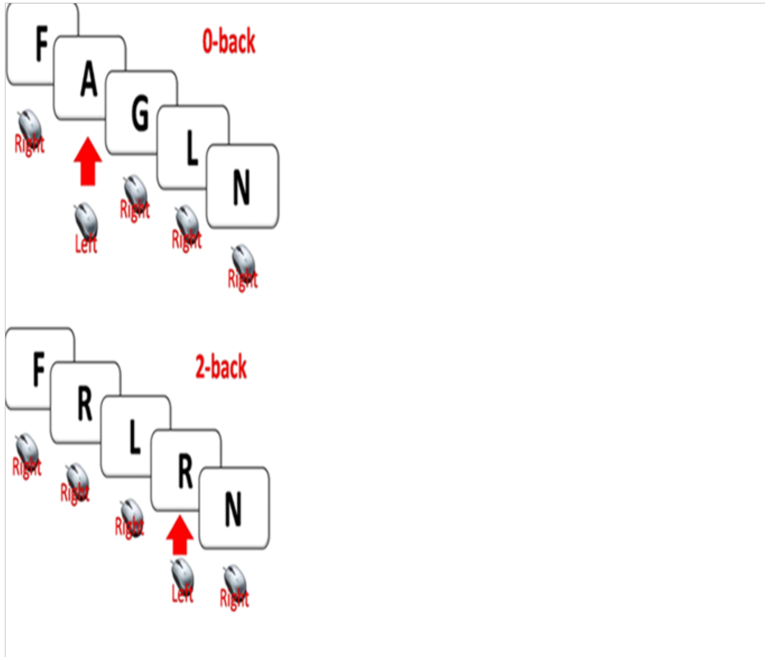
Coordinated unimanual finger-movement in response to exogenous visual stimuli.

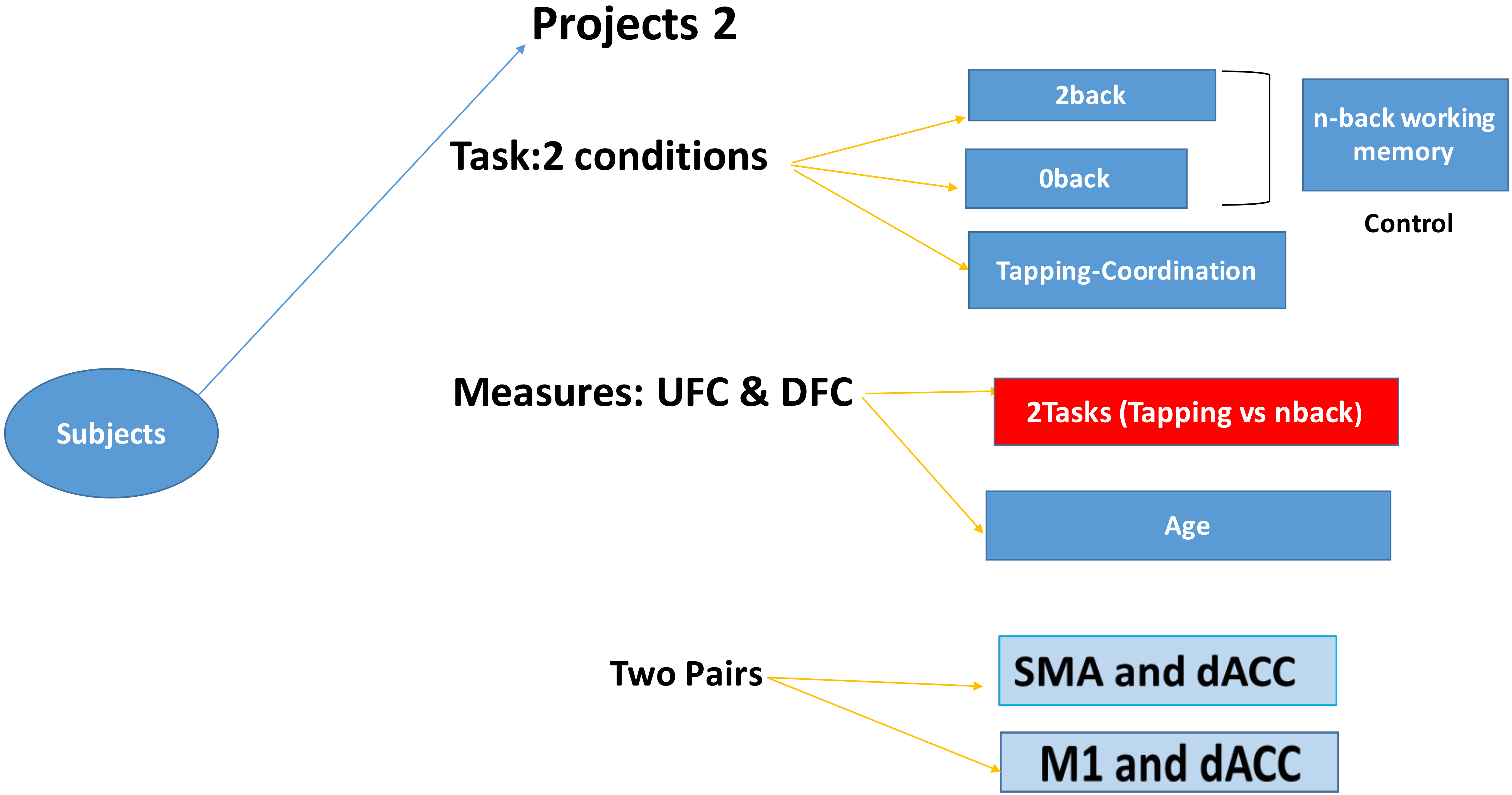
Tapping-Coordination (TP task)

vs

n-back working memory

Control




Projects 2
Task:2 conditions
2back
0back
Tapping-Coordination
n-back working memory
Control
Subjects
Measures: UFC & DFC
2Tasks (Tapping vs nback)
Age
Two Pairs
SMA and dACC
M1 and dACC

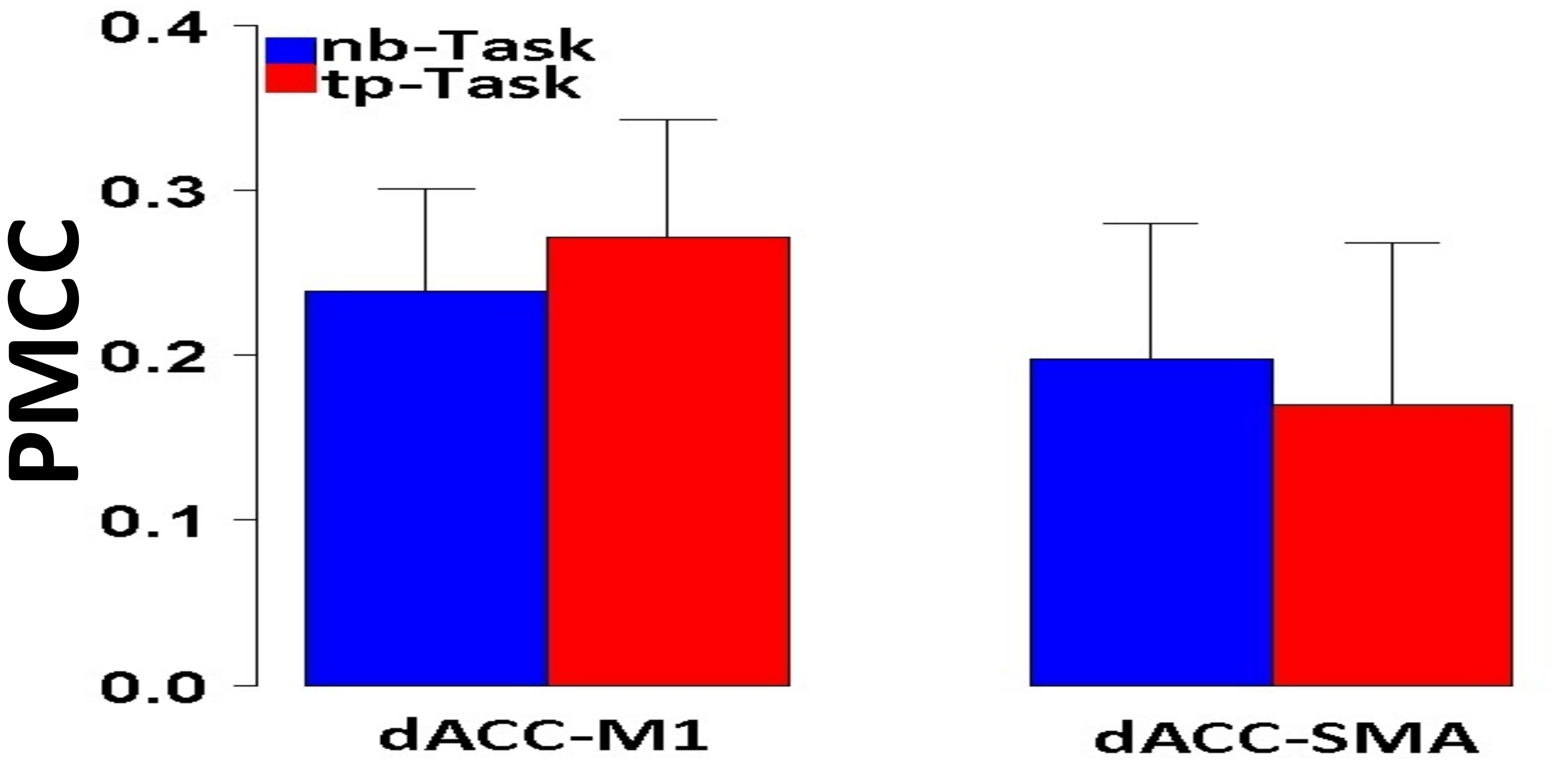
Results

Project 2

a) Undirected Functional Connectivity
b) Directed functional connectivity
c) Age

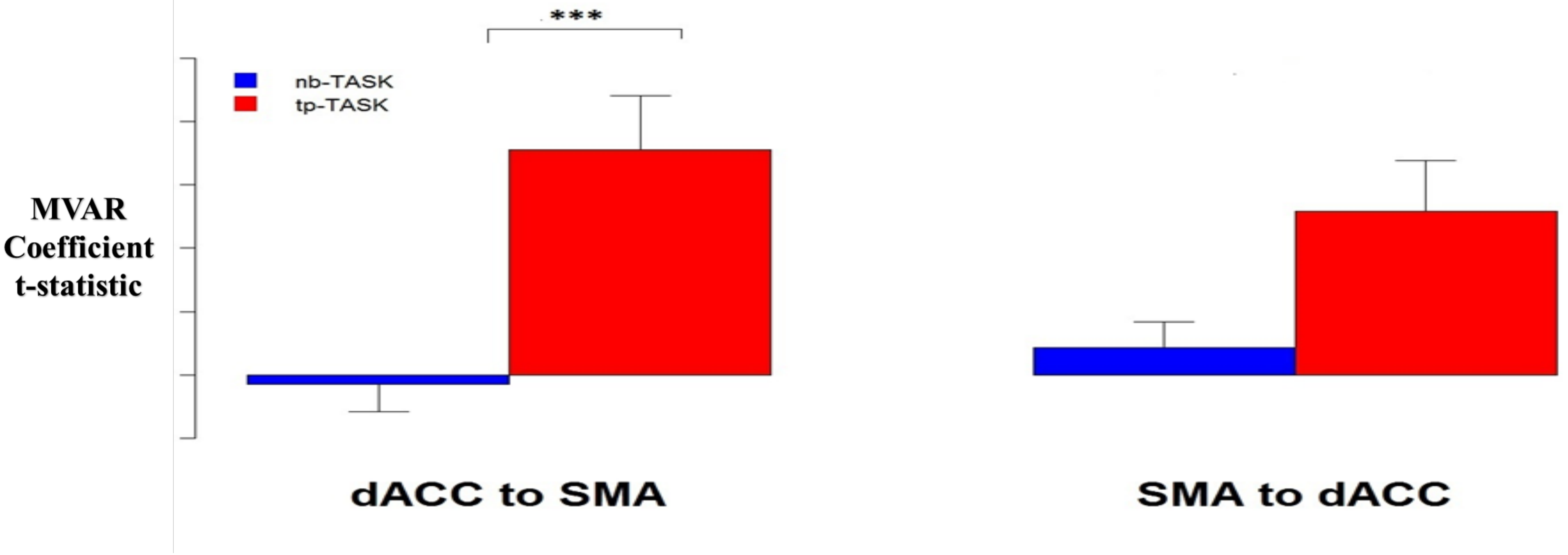
UFC Results

Undirected Functional Connectivity (UFC) :

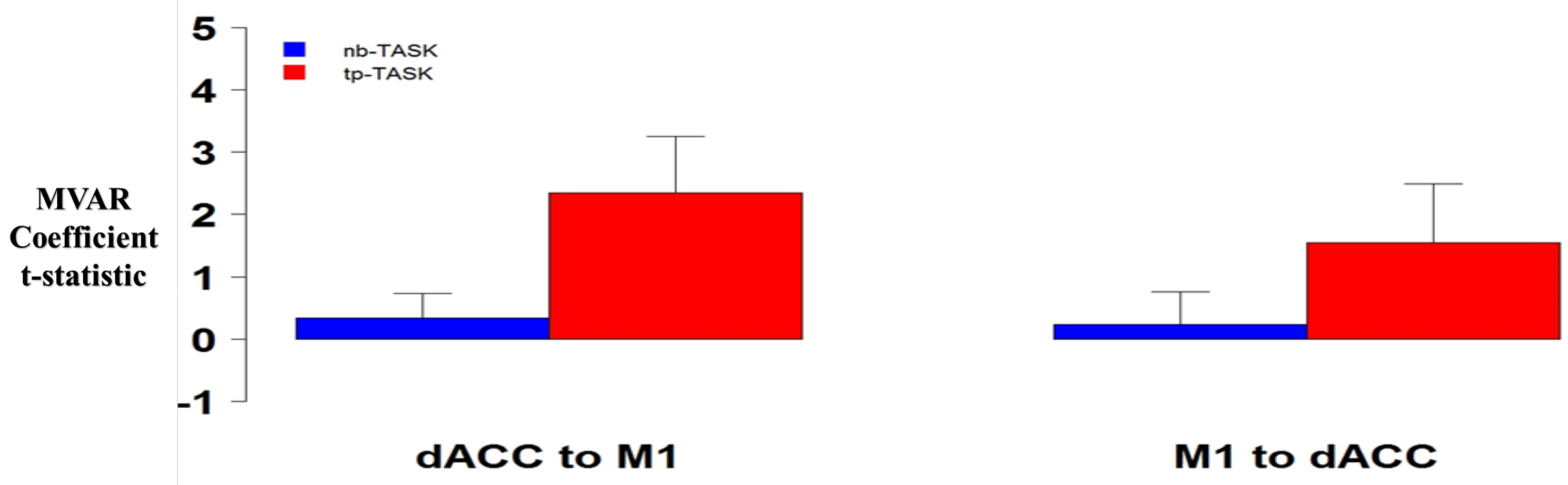


DFC Results

Directed Functional Connectivity (DFC):
The group mean and standard error of influence in both directions between the 2 ROIs (SMA to dACC, dACC to SMA) for nb-task (blue) and tp-task (red) conditions.

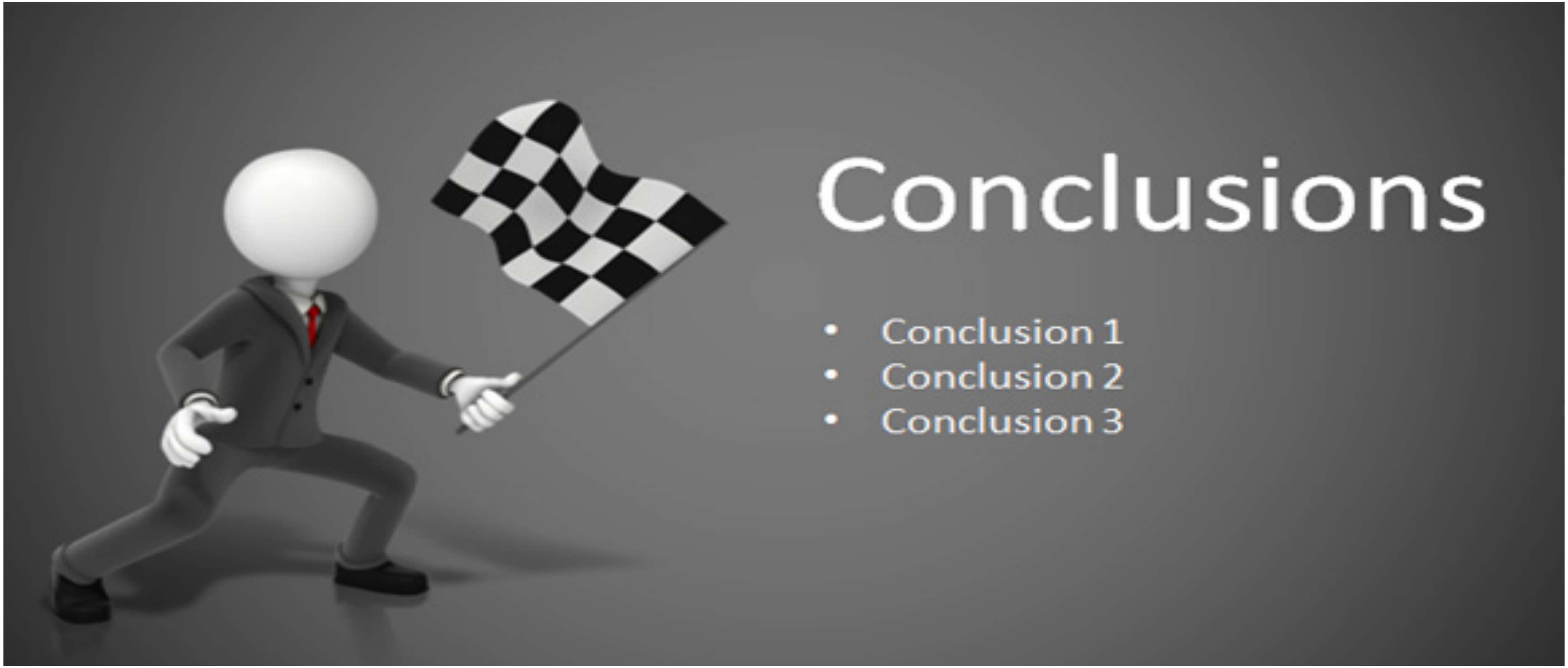


The group mean and standard error of influence in both directions between the 2 ROIs (dACC to M1 , M1 to dACC) for nb-task (blue) and tp-task (red) conditions.



Age results

The task-specific modulatory influence from the dACC to the SMA was independent of age in all conditions.


Conclusions
• Conclusion 1
• Conclusion 2
• Conclusion 3

The dACC is not just involved in motor movement, but has a modulatory role on another motor control region.

- That the directional influence from the dACC to the SMA significantly distinguished task from rest suggests that the dACC may reside at a hierarchically higher organizational level than the SMA in motor control.

- The unimanual visumotor task, in which the dACC selectively modulates the SMA during visually coordinated unimanual behavior in adolescents, showed significantly greater influence from dACC to SMA than in the working memory task, thus suggesting a role for dACC in motor control that is different in the two tasks.

- According to our results, each task (nb-task or tp-task) employed different networks based on the nature of the motor response.

Predictable vs Unpredictable Stimulus in the Coordinated Movement Task

- The dACC activity was more tightly coupled with SMA and M1 when the stimulus was more predictable (Periodic) as compared to when it was less predictable (Pseudo-random).

- The results showed that there is a significant difference between Periodic and Pseudo-random conditions in directed functional connectivity from the dACC to the SMA.

The Maturing of dACC Related to Motor Control

In both studies, we sought to understand if the dACC of healthy adolescents is uniquely involved in motor control.

- Yes, dACC is involved in motor control at the adolescent stage of healthy brain development.
- Motor control, especially in motor coordination is established by the time of adolescence.
- From our study, the role of the dACC as an important brain area for the mediation of task-related motor control is in place during adolescence and may continue into adulthood (Asemi et al., 2015).


Limitation and
future research

We identified 3 limitations in our studies.

Young Age

Our study used adolescent subjects not adults.

Small Sample Size

The number of subjects in this study was small and this limited the number of interactions that could be studied.

Statistical Analysis

Our statistical analysis of time series did not allow us to determine the anatomical pathway over which modulatory signals might be conveyed between areas.

Future Directions

These findings should be of general interest to those studying motor control and neuropsychiatric illnesses in adolescents and adults:

Further testing needs to be done:

i. The role of dACC in motor control in adults.

ii. Coordination (synchronization) vs Continuation in dACC to SMA interaction in adults and adolescents.

iii. Synchronization vs Syncopation in dACC interaction with SMA in adults and adolescents.

iv. Repeat these experiments in adolescent attention deficit hyperactivity disorder (ADHD), adolescent schizophrenia and adolescent Obsessive-Compulsive Disorder (OCD).

The end!

Thank you for your attention!

Any questions?

GC

A. Restricted Model

$$x_t = \sum_{i=1}^{m} \alpha_{1i} \chi_{t-i} + \varepsilon_{1t}$$

$$Var(\varepsilon_{1t}) = \sum\nolimits_1$$

$$F_{\chi \to \Upsilon} = ln \frac{\Sigma_1}{\Sigma_2}$$

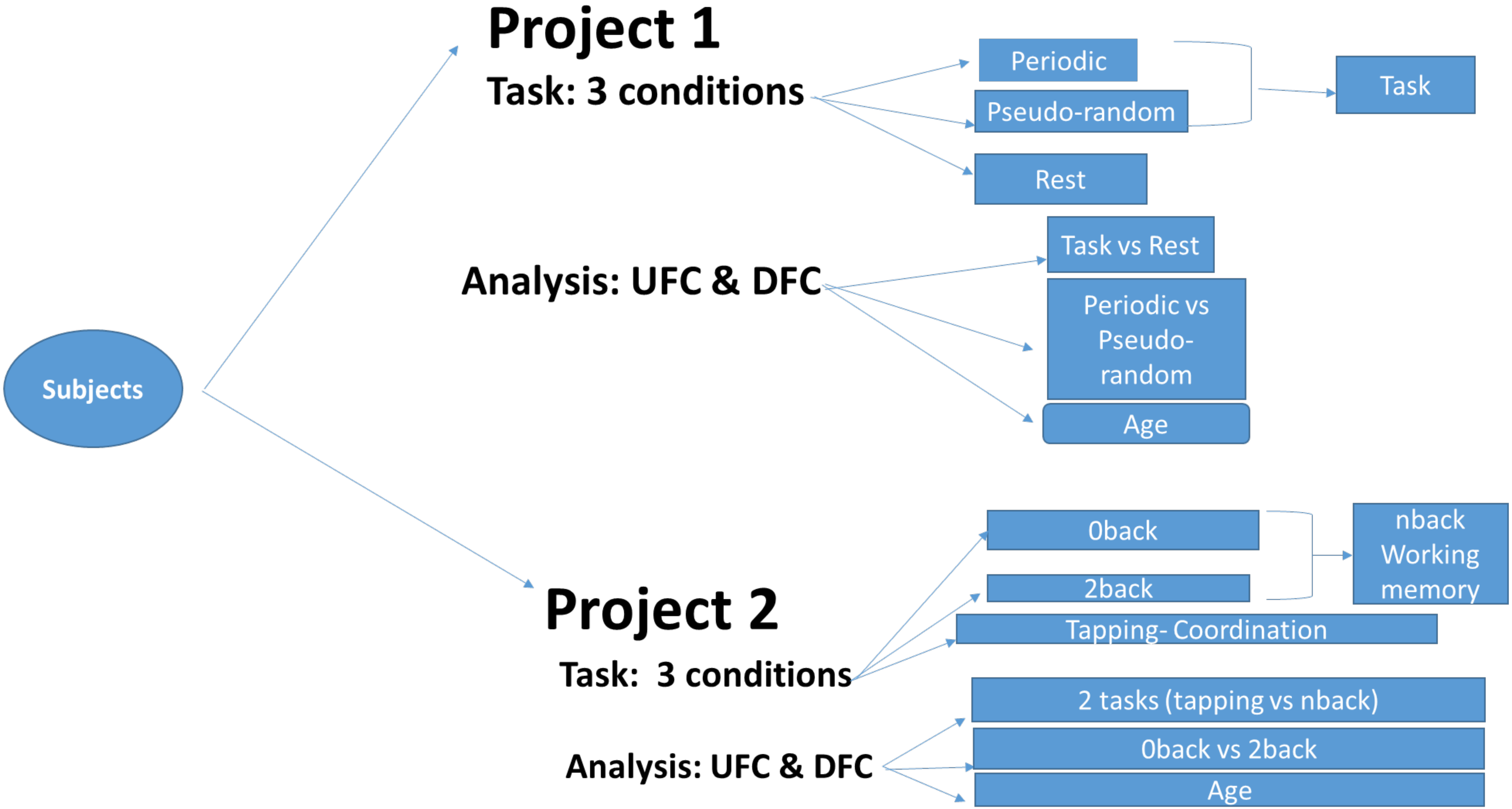
B. Unrestricted Model

$$\chi_t = \sum_{i=1}^{m} \alpha_{2i} \chi_{t-i} + \sum_{i=1}^{m} \beta_{2i} \Upsilon_{t-i} + \epsilon_{2t}$$

$$Var(\varepsilon_{2t}) = \sum\nolimits_2$$

$$\beta_{2i} \neq 0$$

Then Υ & X *granger causes X*


Project 1
Task: 3 conditions
Periodic
Pseudo-random
Rest
Task
Analysis: UFC & DFC
Task vs Rest
Periodic vs Pseudo-random
Age
Subjects
Project 2
Task: 3 conditions
0back
2back
nback Working memory
Tapping- Coordination
Analysis: UFC & DFC
2 tasks (tapping vs nback)
0back vs 2back
Age

$$t_{\hat{\beta}} = \frac{\hat{\beta} - \beta_0}{\mathrm{s.e.}(\hat{\beta})},$$

Functional magnetic resonance imaging (fMRI) :Functional neuroimaging

- To detect correlations between brain activation and a task the subject performs during the scan.

- Based on Blood-Oxygen-Level-Dependent (BOLD):Hemodynamic response (HDR)

- A subject performs a cognitive task-> neurons become active->

deoxyhemoglobin $\uparrow$ -> local blood flow -> oxy-hemoglobin $\uparrow$ ->increase in the fMRI signal

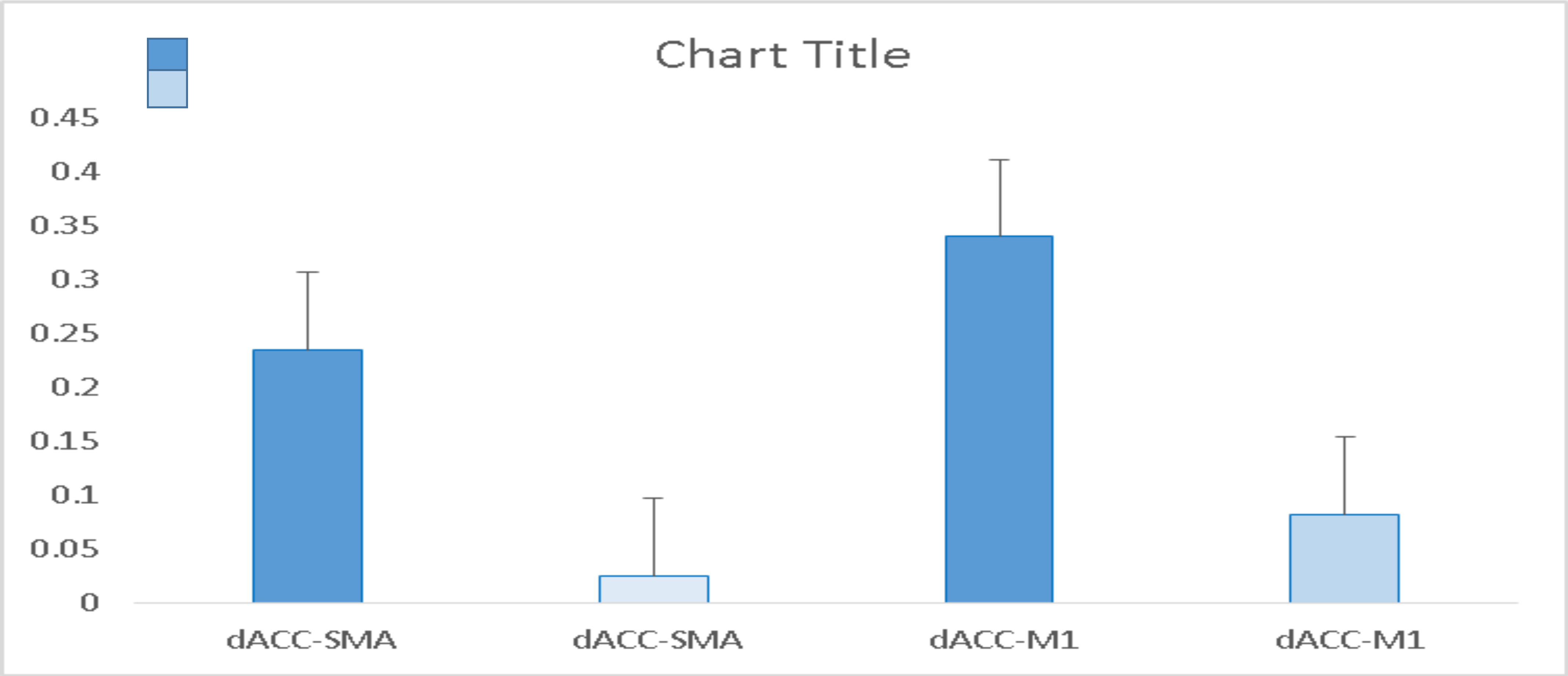
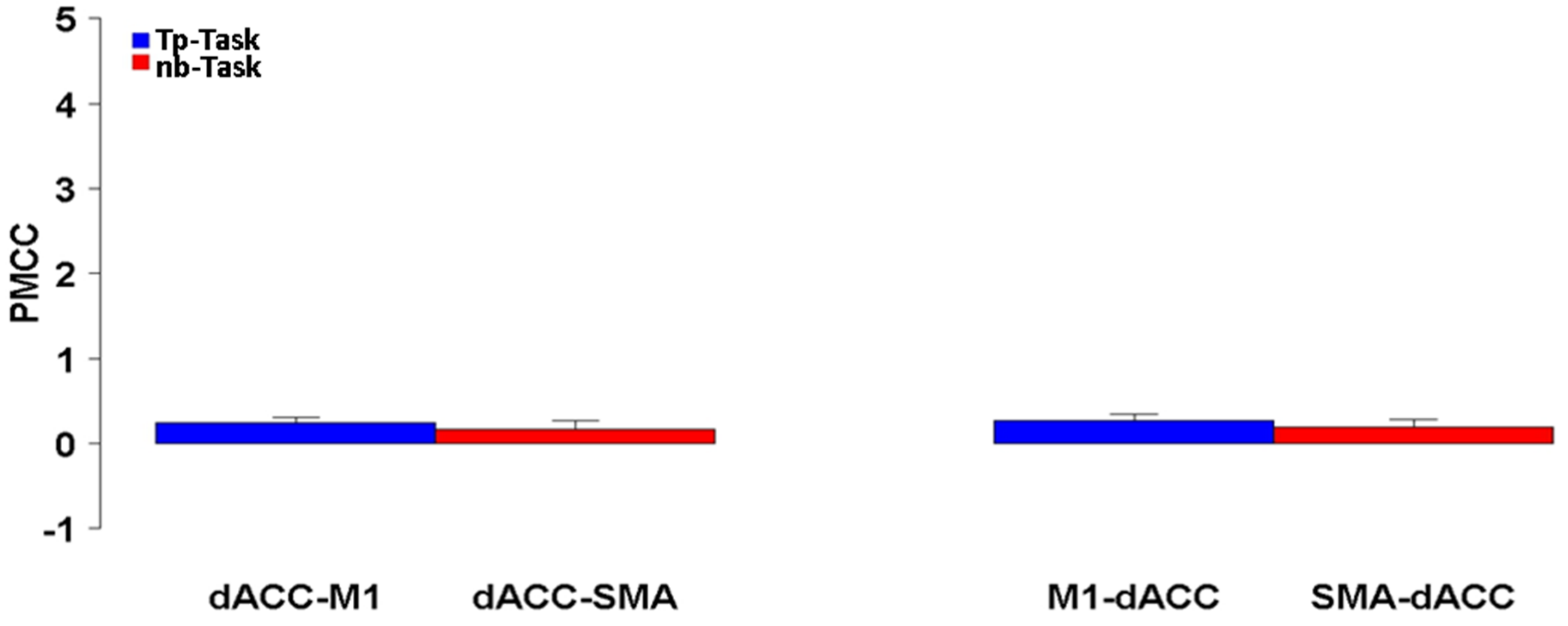


Chart Title
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
dACC-SMA
dACC-SMA
dACC-M1
dACC-M1



PMCC
5
4
3
2
1
0
-1
Tp-Task
nb-Task
dACC-M1
dACC-SMA
M1-dACC
SMA-dACC