Neural Mechanisms of the Freeze-to-Fight Transition

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Primary Objective: The primary objective of the current study is to measure the neural activation involved in transitioning from freeze to fight, in healthy subjects.Secondary Objective(s): To measure connectivity patterns related to freeze and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON40397

Source
ToetsingOnline

Brief title
Freeze to Fight

Condition

- Other condition

Synonym
Anxiety, fearjavascript:saveABR('C')

Health condition

The study is not primarily aimed at a disease but normal neural and cognitive function. It is secondarily related to anxiety and aggression.

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: The ERC Starting Grant "Neural control of human freeze-fight-flight" of Karin Roelofs

Intervention

Keyword: Fight/Flight, fMRI, Freeze

Outcome measures

Primary outcome

The main study measurement is the contrast between BOLD responses for the various task conditions. We will also measure effective connectivity in brain activity, heart rate, heart rate variability, pupil dilation, and behaviour (body sway, reaction time and accuracy) during the different conditions of the task.

Secondary outcome

Not applicable.

Study description

Background summary

Upon encountering a threat, a state of attentive immobility called the freeze response can be evoked. This response has been argued to serve various functions: to avoid detection by a predator or triggering an attack, to prepare for the fight or flight response, and to accumulate information determining whether to break out freeze, and if so whether the fight or the flight response will be selected. During freeze parasympathetic activity is dominant, causing for instance a decrease in heart rate termed *fear bradycardia*. The transition from passive freeze to active fight-or-flight involves sympathetic activation and a heart rate increase (Fanselow, 1994). The ability to transition from passive freeze to active fight/flight when appropriate is critical for survival (Blanchard ea, 2011). How does an organism decide that it is time for an active response? Recent observations suggest that the apparent rules of freeze and

fight/flight in animal may also apply to human defensive responses: 1) Specific defenses associated with specific threats are shared by lab rats and humans; 2) Specific components of freeze and fight-or-flight are differentially affected by distinct pharmacological interventions; 3) Outcome of freeze-related risk assessment (fight-or-flight) is stable across new and old situations in men and rodents (Blanchard ea 2011; Korte ea, 2005).

The neural mechanisms of transitioning from freeze to defensive action in humans remain largely unknown. Studies in rodents have shown that the amygdala plays a key role in orchestrating defensive behavior and transitioning between defensive modes (Ledoux, 1988). Whereas freeze involves direct projections from the amygdala to the brainstem (periaquaductal gray: PAG), active (fight/flight) responses depend on amygdala projection to the ventral striatum, were dopaminergic projections facilitate active fight/flight responses (Ledoux, 1988). Testosterone has been suggested to promote the transition from freeze to active fight/flight by acting on those dopaminergic projections in the striatum (De Souza ea, 2009; Hermans ea 2010). The aPFC is involved in regulating the amygdala and striatum-driven actions via top-down control (Volman ea, 2011). The study of the role of these regions in freeze-fight transitions in humans has been thwarted by technical challenges. The size and location of the periaquaductal gray (PAG), that plays a central role in models of defensive reactions, preclude the use of traditional fMRI protocols, as the signal may be confounded by motion artefacts associated with heart pulse affecting local blood vessels. However in a recent pilot study, it has been shown that these artefacts can be controlled for, neural correlates of fear bradycardia during aversive versus neutral picture viewing can be detected. This showed a negative correlation between heart rate frequency and PAG activity. In addition, there was strong amygdala-brainstem connectivity associated with the fear bradycardia, providing the first evidence that similar amygdala-brainstem projections may facilitate freeze-like behavior in humans as in animals. These findings lay the grounds for investigations of the neural correlates of human freeze behavior, and most importantly, of the transition from freeze to active defense responses.

Study objective

Primary Objective: The primary objective of the current study is to measure the neural activation involved in transitioning from freeze to fight, in healthy subjects.
Secondary Objective(s): To measure connectivity patterns related to freeze and fight-preparation; to determine correlations between various physiological measures (including heart rate, body sway, and brain activation) during different task conditions; and to help determine the optimal version of a freeze-to-fight/flight task for a future longitudinal study.

Study design

The study design for the primary research objective is a within-subject full factorial design with healthy adult subjects. Subjects will perform a Shooting Task during a one-hour behavioural session and a subsequent one-hour fMRI scanning session. The Shooting Task will involve two primary experimental factors: a freeze versus no-freeze state, and movement preparation versus no movement preparation. The study is expected to be completed within six months, and will be performed at the Donders Centre for Cognitive Neuroimaging.

Subjects will undergo the following measurement procedure. First, subjects will receive and information brochure and, after signing an informed consent form, be screened to determine if they can participate in fMRI research. At the lab, subjects will fill in the questionnaires. They will then practice the Shooting Task outside the scanner, while standing on a balance board to measure body sway. After that the scanning procedure starts, consisting of an anatomical scan and functional scans during performance of the Shooting Task. When the subject is *shot* during the Shooting Task, out of the scanner a brief burst of white noise will be presented, and in the scanner a mild electric shock will be presented.

Because of the secondary aim of piloting versions of the task for an upcoming longitudinal study, we aim to pilot three versions of the Shooting Task.

Study burden and risks

The burden consists of the time and effort involved in performing the tasks during the measurement session, and experiencing the aversive stimuli (brief bursts of loud noise and electric shocks). There is no expected benefit beyond the compensation and personal interest (as many subjects will be students).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy, adult subjects aged 18 to 34.

Exclusion criteria

- Abnormal hearing or (uncorrected) vision.
- Average use of more than 3 alcoholic beverages daily.
- Average use of psychotropic medication or recreational drugs weekly or more.
- Inability or significant difficulty to cease smoking for 24 hours prior to testing.
- Use of psychotropic medication, or of recreational drugs over a period of 72 hours prior to each test session, and use of alcohol within the last 24 hours before each measurement.
- Metal objects in or around the body (braces, pacemaker, metal fragments, hearing devices).
- Prior or current psychiatric or neurological treatment or current psychiatric treatment.
- History of autonomic failure (e.g., vasovagal reflex syncope).
- Claustrophobia.
- Intense daily physical exercise.
- History of cardiovascular disease.
- Current stressful episode or major life event

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-02-2014
Enrollment:	72
Type:	Actual

Ethics review

Approved WMO

Date:	06-03-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL47093.091.13