Neuroscience and Biobehavioral Reviews 76 (2017) 29–38

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

Immobility reactions under threat: A contribution to human defensive cascade and PTSD

E. Volchan[a,*], V. Rocha-Rego[a,b], A.F. Bastos[a], J.M. Oliveira[a,b], C. Franklin[b], S. Gleiser[b], W. Berger[b], G.G.L. Souza[d], L. Oliveira[c], I.A. David[c], F.S. Erthal[a], M.G. Pereira[c], I. Figueira[b]

[a] Instituto de Biofisica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Brazil
[b] Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Brazil
[c] Instituto Biomédico, Universidade Federal Fluminense, Brazil
[d] Instituto de Ciências Exatas e Biológicas, Universidade Federal de Ouro Preto, Brazil

ARTICLE INFO

Article history:
Received 27 September 2016
Received in revised form 18 January 2017
Accepted 21 January 2017
Available online 25 January 2017

Keywords:
Defensive cascade
Stabilometry
Posture
Body sway
Heart rate
Heart rate variability
Motor reaction
Pictures
Trauma script
Gun violence
Threat
PTSD
Tonic immobility
Attentive immobility
Immobility under attack
Freezing
Humans
RDoC

ABSTRACT

Violence exacts a burden on public health. Gun violence is a major trigger for motor defensive reactions in humans and post-traumatic stress disorder (PTSD) is its main psychiatric sequela. However, studies of the human defensive cascade, especially the motor reactions, are at an early stage. This review focuses on studies that employ stabilometry, a methodology that assesses whole body motor reactions, to address defensive behaviors to violence-related threats. Special attention is given to three reactions: “attentive immobility”, “immobility under attack” and “tonic immobility”, with emphasis on the latter – a peritraumatic reaction which has been strongly associated with the severity of PTSD. These reactions are characterized by reduced body sway and bradycardia, except tonic immobility that presents robust tachycardia. The advances made by investigations into the immobility reactions of the human defensive cascade contribute to helping to bridge the gap between human and non-human species. Furthermore, progresses in basic research to objectively monitor motor defensive reactions under threat can help to develop a dimensional, trans-diagnostic approach to PTSD.

Contents

* Corresponding author at: Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Av. Carlos Chagas Filho 373, Rio de Janeiro 21941-902, Brazil.
E-mail addresses: evolchan@biof.ufrj.br, elivolchan@gmail.com (E. Volchan).

http://dx.doi.org/10.1016/j.neubiorev.2017.01.025
0149-7634/

1. Introduction

1.1. Violence

In 1996, the Forty-Ninth World Health Assembly declared violence a major and growing public health problem across the world (World Heath Assembly, 1996). Six years later, the World Health Organization launched the first report on violence and health aimed at raising awareness about the problem of violence globally, its prevention and the role of public health in addressing its causes and consequences (Krug et al., 2002). In 2014, the World Health Organization, jointly with the United Nations Development Program and the United Nations Office on Drugs and Crime, published the Global Status Report on Violence Prevention (World Health Organization, 2014) which reviewed violence prevention efforts in countries, and called, among other strong recommendations, for the enhancement of services for the victims of violence.

Apart from being a cause of death, violence exacts an enormous burden on public health with extremely deleterious consequences, particularly from gun violence (Webster et al., 2016). The toll of gun violence is not just premature death but a series of serious snowball effects on education, health, family instability, incarceration, and social capital (Winker et al., 2016).

1.2. Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is the main psychiatric sequela from exposure to traumatic events such as gun violence. Presently, the trigger of PTSD is considered to be exposure to actual or threatened death, serious injury or sexual violation. For the diagnosis of PTSD, in addition to the exposure to one or more of those potentially traumatic events, the DSM-5 requires that a given person presents, for at least one month, symptoms of intrusion, persistent avoidance of stimuli, negative alterations in cognitions and mood, and alterations in arousal and reactivity, all of them related to the traumatic event. Similarly to other DSM-5 diagnosis, symptoms must create distress and/or functional impairment (American Psychiatric Association, 2013).

However, since at its conception, PTSD diagnosis has been surrounded by controversy (Miller et al., 2014). This controversy has further increased with the revision of the PTSD criteria in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which has expanded the construct to include additional symptom presentations (American Psychiatric Association, 2013). In DSM-IV (American Psychiatric Association, 1994) there were 17 PTSD symptoms, divided in three clusters: intrusive re-experiencing, avoidance/numbing, and hyperarousal. This allowed various combinations of required symptoms to meet the PTSD diagnosis, resulting in a total of 79,794 possible symptom presentations. DSM-5 increased the number of symptoms from 17 to 20, and the number of clusters from three to four with the addition of alterations in mood and cognition, raising the number of possible symptom presentations meeting the PTSD diagnosis from 79,794 to 636,120 (Galatzer-Levy and Bryant, 2013). As a consequence, the new PTSD definition is much more heterogeneous than before, and also more heterogeneous than the majority of the other DSM psychiatric disorder such as panic, social phobia, or major depression. In fact, PTSD research has been plagued by lack of replication, mixed findings, and poor specificity despite massive research funding and intensive investigative efforts. The main factor that may explain the disappointing lack of progress in this field is the heterogeneity derived from the different clinical manifestations of PTSD that may impede progress in the identification of the biological underpinnings of this disorder (Nemeroff et al., 2013).

1.3. The Research Domain Criteria

The heterogeneity found in PTSD diagnosis using DSM is an example of a research obstacle that has led the National Institutes of Mental Health (NIMH) to develop the Research Domain Criteria (RDoC) (www.nimh.nih.gov/research-priorities/rdoc/index.shtml), a research framework which adopts a trans-diagnostic approach (Cuthbert, 2014; Galatzer-Levy and Bryant, 2013; Insel et al., 2010). This change in focus by NIMH reflects the concern that research based on DSM diagnoses are limited due to their primary focus on reliability at the expense of validity – leading to scientifically inconsistent findings. The RDoC project considers it fundamental to capture the underlying mechanisms of dysfunction, opening new possibilities for treatments targeted to pathophysiological mechanisms. The RDoC project extends the categorical view of mental illness diagnosis, and suggests an dimensionality to mental disorders, as a spectrum that ranges from normal to abnormal. It also focuses on the underlying mechanisms (psychological, behavioral, physiological, the neural circuit framework, etc.) that cut across a wide array of psychiatry manifestations, operating outside the traditional diagnostic boundaries. Therefore, the RDoC takes a translational, dimensional approach to defining psychopathology, and aims to promote the development of an interdisciplinary science of psychopathology that consists of dimensional constructs integrating elements of psychology and biology (Kozak and Cuthbert, 2016). An objective of this approach is to develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures (NIMH, 2016).

In line with the RDoC initiative, we developed a research project associated with the outpatient clinic of the Federal University of Rio de Janeiro (Brazil) specializing in PTSD assessment and the treatment of victims of urban violence. The research team comprises a multi-disciplinary group of researchers from different fields including: basic neuroscience, psychophysiology, psychiatry, psychology and epidemiology. In the present mini-review, part of the results gathered by this network will be considered.

The RDoC project identified five research domains (negative valence, positive valence, cognitive, social processes, arousal and regulatory systems) within which the "negative valence systems" domain is the one more closely related to our research focus.

This domain was classified into constructs that involve responses to acute threat, potential harm, sustained threat, frustrative non-reward, and loss (see Kozak and Cuthbert (2016)). The studies reviewed here are connected to defensive reactions to violence-related threat and mainly relate to the constructs of acute and sustained threat.

1.4. Defensive reactions to violence-related threat

Assaultive violence with a gun is a major trigger for motor defensive reactions in humans. The impact of gun-related violence on the brain was studied by Rocha-Rego et al. (2012) employing structural magnetic resonance imaging in patients from our university clinic, who were diagnosed with PTSD.

A robust reduction of gray matter volume in the ventral premotor cortex in victims with PTSD compared to victims without PTSD was observed. Electrophysiological studies in non-human primates (Graziano and Cooke, 2006) revealed a region within the premotor cortex which is involved in the representation of the peripersonal space and in the selection and coordination of defensive behavior. The peripersonal space can be defined as a margin of safety around the body or a flight zone (Hayduk, 1978; Horowitz et al., 1964; Lloyd, 2009), the shape of which is plastic and dynamic, changing in different surroundings and contexts (Cléry et al., 2015; Holt et al., 2014). Abnormalities in the ventral premotor cortex of the PTSD patients (Rocha-Rego et al., 2012) may be related to a disruption in the dynamic modulation of the peripersonal space and to inefficient selection and coordination of motor defensive reactions during and in the aftermath of the violent events.

Despite their fundamental importance to the understanding of resilience and vulnerability for PTSD associated with violence-related trauma, studies of motor defensive reactions in humans are still in the early stages. This is not the case in works on non-human species, which have shown that threats from predators or con-specifics prompt a cascade of hard-wired defensive behaviors including overt actions and/or immobility. Potential threat evokes attentive immobility; predator attack evokes flight, when escape is available; and aggressive defense, when prey-predator distance shortens (Marks, 1987; Ratner, 1967). When escape routes are blocked, and the predator approaches, immobility and/or aggressive threats ensue (Blanchard and Blanchard, 1989, 1971; Blanchard et al., 1986). When survival is extremely threatened, tonic immobility is the last anti-predator resort (Marks, 1987; Ratner, 1967). It is worth mentioning that external factors, such as the predator species, its behavior and proximity, as well as the particularities of the surrounding contexts, all play a part in triggering a particular defensive response. Internal factors are also important and include species-related strategies, individual variability in defensive predispositions within species, past experiences undergone by each individual (Eilam, 2005; Korte et al., 2005).

Motor reactions, either overt actions or immobility, are the core of the observable defensive behaviors. We have made successful attempts to advance the knowledge of the defensive cascade in humans through studies of whole body motor reactions to threats (Azevedo et al., 2005; Bastos et al., 2016; Facchinetti et al., 2006; Volchan et al., 2011). The methodology used to address this issue was stabilometry, a useful technique to study body sway.

In the present mini-review, we will focus on studies that employed stabilometry to address the defensive reactions to violence-related threats. Special attention will be given to immobility reactions[1] with an emphasis on tonic immobility, a peritraumatic reaction which has been strongly associated with the severity of PTSD caused by violent traumatic events (Fiszman et al., 2008; Lima et al., 2010; Rocha-Rego et al., 2009).

[1] Other defensive repertoires such as risk assessment and aggressive defense will not be addressed here.

1.5. Stabilometry: a brief description

Standing balance involves continuous and intermittent activity of muscles distributed over the whole body to maintain dynamic equilibrium with respect to the environment. This is accomplished by the resulting motor outputs of complex brain processes involving information from several sensorial inputs including the proprioceptive, visual and vestibular systems (Balasubramaniam and Wing, 2002; Diener et al., 1986).

Stabilometry is a technique employed to study the body sway of human participants in a standing position using a force platform. A force platform is a device that uses a set of force transducers to quantify the ground-reaction vector force and determine its point of application, known as the center of pressure. Usually, the device is connected to a computer which records the displacement of the center of pressure for a preset period of time. A statokinesigram is the graphic representation of this displacement, presented in the horizontal plane (Fig. 1). The displacement of the center of pressure can also be visualized as a stabilogram, a representation of the statokinesigram projected in one axis, either anterior–posterior or lateral–lateral, as a function of time.

Global amplitude of body sway over a period of time can be extracted from the statokinesigram. A typical parameter is the sway area estimated by the computation of an ellipse enclosing most of the points on the center of pressure path. From the stabilograms, it is possible to extract, for example, amplitude (standard deviation) and frequency parameters related to the projection of body sway in either the anterior-posterior or lateral-lateral axes (Kapteyn, 1972; Prieto et al., 1993).

The statokinesigram represents the participant's motor strategies to keep his/her upright body in balance over a certain period of time and under a certain condition. External (and internal) challenges add to this dynamic, preparing the body for behavioral (re)actions.

2. Immobility defensive responses

Three immobility defensive responses are described: "attentive immobility", "immobility under attack" and "tonic immobility". The word "freezing" is commonly used in reference to defensive immobility in the literature (see Hagenaars et al. (2014)). Freezing has been used interchangeably in the descriptions of different kinds of immobility responses to threat, rendering it misleading and difficult to make comparisons between studies. For that reason, we will not adopt this term in the present review.

2.1. Attentive immobility

The fast, effortless processing of potentially threatening stimuli is highly advantageous and may be critical for survival. When an animal detects a predator but has not been spotted (a potential threat), attentive immobility is a common adaptive defensive behavior (Fig. 2A). Being motionless increases the chances of going unnoticed by a predator, and can be an efficient strategy if employed before the prey is spotted by the predator (Eilam, 2005; Marks, 1987; Ratner, 1967). Upon detecting cues associated with potential threat, the alerted individual can become abruptly motionless, monitoring the source of danger, and ready to switch to another behavioral strategy.

Campbell et al. (1997), using implanted biotelemetry devices in non-humans species, observed immobility and bradycardia in response to potential threat. Taking those results in account, Lang et al. (1997) designed experimental paradigms to draw an analogy

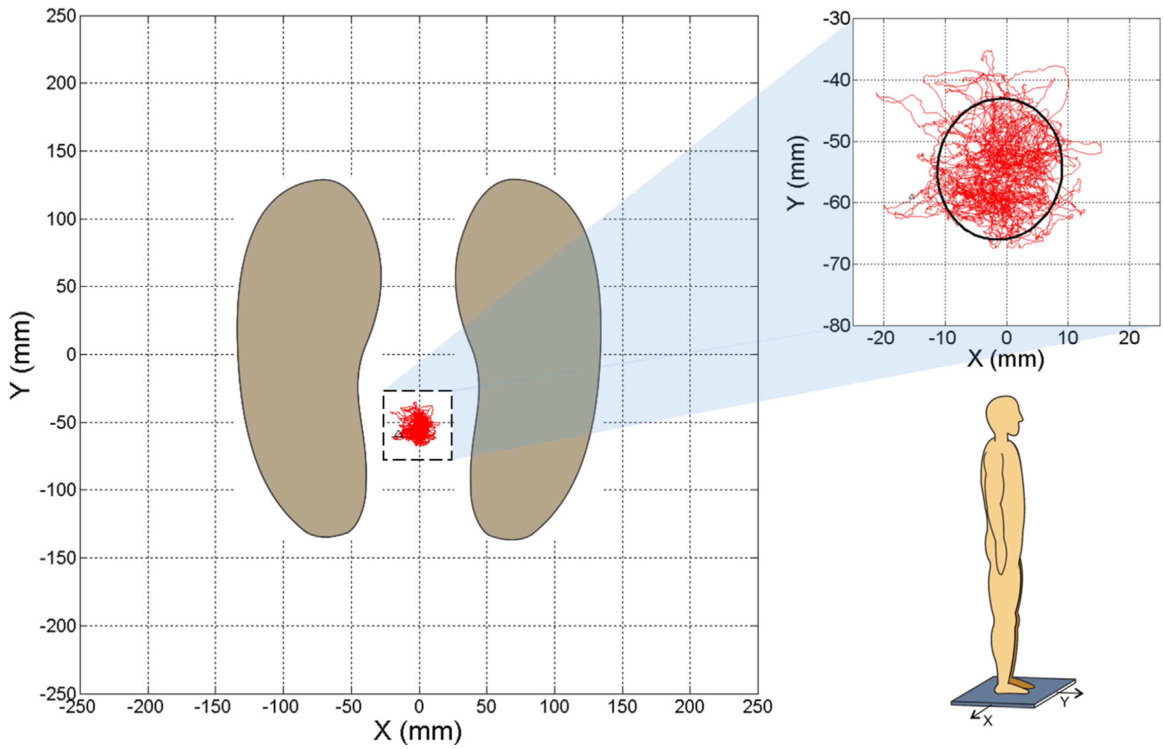

Fig. 1. Statokinesigram: displacement of the center of pressure. On the left, a schematic top view of a force platform illustrating the feet position of a participant. In red, a depiction of the path of his/her respective center of pressure, representing body sway during a given period of time. The path of the center of pressure is shown enlarged on the upper right side. An ellipse shown in black, enclosing most of the points on the center of pressure path, is computed for the calculation of the sway area. On the lower right side a schematic human figure standing on a force platform is shown. Y: anterior-posterior direction, X: lateral-lateral direction.

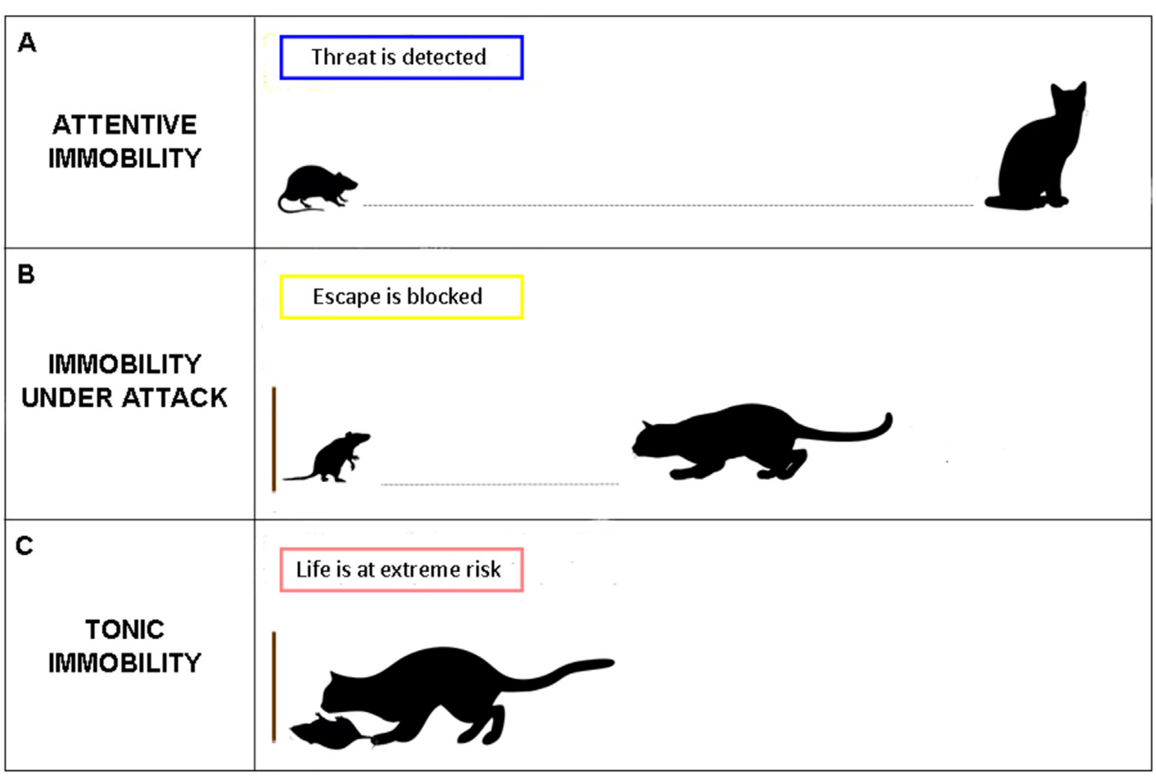

Fig. 2. Schematic representations of immobility defensive reactions in non-human mammal. (A) Attentive immobility is a typical reaction when an animal detects a potential threat, but has not been spotted by the predator. (B) Immobility under attack may occur when the prey detects signs of imminent attack and an escape route is not available. (C) Tonic immobility is the last defensive resort when life is at risk and survival is extremely threatened. Note that flight under attack when an escape route is available is not represented in this figure.

for attentive immobility in humans. The authors used aversive pictures to represent potential threat. Exposure to them was found to prompt cardiac deceleration, as well as moderate increased skin conductance, potentiated startle reflexes, and reports of high arousal and unpleasantness (Bradley et al., 2001). Immobility in humans was not probed.

The work of our team (Azevedo et al., 2005; Facchinetti et al., 2006), using stabilometry, allowed immobility reaction during viewing of aversive pictures to be more closely characterized for the first time. During the experimental session, participants stood on a force platform with their feet together and arms along their trunk, and looked at a monitor while body sway was recorded. They also had sensors attached to record the electrocardiogram. The statokinesigrams and stabilograms were analyzed to extract amplitude parameters – area and standard deviations in lateral–lateral and anterior-posterior axes. Mean power frequency was also analyzed for both axes. In the two studies (Azevedo et al., 2005; Facchinetti et al., 2006), mutilation pictures and neutral control ones were presented, both categories in a separate full sequence without intervals. Pictures of injured humans represented cues for potential threats. The results revealed a reduced area of sway, signaling less mobility. In both studies reduced amplitude was more evident in the lateral–lateral axis; accompanied by "rigidity", characterized by augmented mean power frequency in the same axis, and by bradycardia.

Taken together, these findings are objective signs of a defensive reaction that could be analogous to the attentive immobility described in other species. Interestingly, individual variability was shown to influence this defensive reaction. A study from another group (Hagenaars et al., 2012), using a paradigm similar to Azevedo et al. (2005), showed that the number of prior aversive life events affected the magnitude of the immobility reaction.

This experimental design, that allowed the recording of subtle and automatic changes in whole body motor reactions upon detecting threatening cues, opened an avenue for further examining the defense cascade in humans.

2.2. *Immobility under attack*

When the prey detects signs of imminent attack, the defensive strategy usually switches to flee. However, as demonstrated in a series of experiments (Blanchard and Blanchard, 1971; Blanchard et al., 1986); when escape is blocked, a different type of immobility reaction, under attack, may occur (Fig. 2B).

Blanchard et al. (2001) devised a paradigm in which human participants should select from a list of choices the defensive behavior they would adopt if faced with different threatening scenarios (see also Perkins and Corr, 2006; Shuhama et al., 2008). Escaping was chosen as the most likely response to scenarios evaluated as unambiguous and highly threatening, when an escape route was available; and become immobilized was chosen in an inescapable threatening situation.

To measure these reactions through body sway recording, our team conceived an experimental design employing clear-cut threatening pictorial stimuli, in which clues of an escape route were either present or absent (Bastos et al., 2016). To simulate attack-like threat, pictures depicting a man carrying a gun were used. Moreover, the majority of the participants reported having been previously exposed directly or indirectly to violent crime, which made the pictures even more relevant to the sample. In pictures simulating possibility of escape, the gun was directed away from the participant; in those simulating higher risk and less chance of escape, the gun was directed toward the participant. Matched control pictures depicted similar layouts, but with the gun substituted for a non-lethal object (e.g. a camera). Pictures within each category were presented in a full sequence without intervals. Participants stood upright on the force platform and looked at a monitor. Stabilometry and electrocardiography were recorded. After the recording session, participants evaluated the emotional impact of each set of pictures.

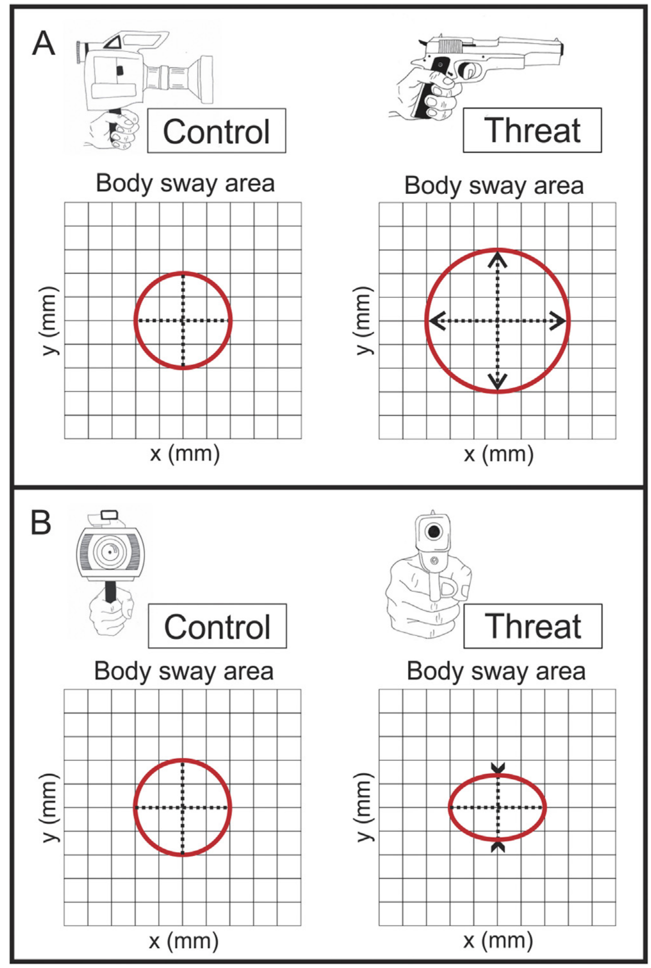

Fig. 3. Schematic statokinesigrams representing the area of body sway during the viewing of control pictures and threat pictures. (A) Cues for the presence of an escape route (pointed away). Non-lethal object pointed away from the observer (control) and gun pointed away from the observer (threat). Amplitude of body sway area is increased for threat compared to control pictures, conceivably representing a transition into a more active motoric state in preparation to escape. (B) Cues for the absence of an escape route (pointed toward). Non-lethal object pointed toward the observer (control) and gun pointed toward the observer (threat). Amplitude of body sway is reduced in the anterior-posterior axis for threat compared to control pictures. The reduction in back-and-forth sway in response to pictures of a pointed gun (less possibility of escape) evokes an "immobility under attack" reaction.

Bastos et al. (2016) observed that pictures depicting a man carrying a gun compared to matched control pictures (non-lethal objects) were evaluated as more intense and with more risk of death, and triggered more desire to escape. Compared to the pictures in which the gun was pointed away from the participant, the pictures in which the gun was directed toward the participant were evaluated as more threatening, closer, with less chance of escaping and with less chance of hiding. Also, pictures with the gun directed at the participant were perceived as less ambiguous and presenting increased risk of death with participants reporting feeling immobilized, and with more desire to escape.

For the pictures that simulate threat with more possibility of escape, with the gun directed away from the participant, postural reactivity was characterized by a general increase in the amplitude of body sway, compared to matched control pictures (Fig. 3A). Exposure to gun directed-away pictures did not evoke a bradycardic effect as it did when participants were exposed to pictures of mutilation (Azevedo et al., 2005; Facchinetti et al., 2006), in fact, there was some indications of heart rate drift toward acceleration (Bastos et al., 2016). In the case of pictures depicting guns directed away from the participant presented to a sample with a history of prior exposure to violence, instead of yielding attentive immobility they seemed to trigger a predisposition to a more active motoric state, possibly an escape-like defensive response.

Exposure to pictures portraying the gun directed toward the participant, which were evaluated as the most threatening and presenting the least chance of escaping, resulted in different postural and cardiac reactions (Bastos et al., 2016). Compared to the presentation of matched pictures of non-lethal objects, there was a significant reduction of the amplitude of body sway in the anterior-posterior axis (Fig. 3B) and bradycardia. This reaction resembles the immobility under attack described in non-human animals under exposure to a predator and with escape routes blocked (Fig. 2B).

In conclusion, the results from Bastos et al. (2016) indicate that when exposed to threat in a context indicating a possible escape route, humans, as in non-human species, engage in active escape (increased body sway), resembling the flight stage of the defensive cascade. When facing threat with less possibility of escape, results indicate that humans present immobility under attack – a specific immobile response (reduced back-and-forth sway) with bradycardia.

Although there are somatic and autonomic similarities between “attentive immobility” and “immobility under attack”, the contexts that evoke each of these evolutionary adaptive strategies are clearly distinct. In the former, there is no sign of current attack; while in the latter, the attack is ongoing and an escape route is not readily accessible.

2.3. *Tonic immobility*

When life is at extreme risk, tonic immobility is the last defensive resort. It is a reflexive and involuntary reaction, elicited under the perception of overwhelming danger, and is characterized by reversible profound motor inhibition (Fig. 2C) and relative unresponsiveness to external stimuli (Ratner, 1967). Tonic immobility is of adaptive value under predation attack (Rütting et al., 2007; Sargeant and Eberhardt, 1975), since a predator may loosen its grip to hide the prey or to fend off other predators.

2.3.1. *Systematic retrospective reports*

Although described in non-human animals for more than three centuries (Maser and Gallup, 1977), it was not until 1979 that Suarez and Gallup (Suarez and Gallup, 1979) argued that there were similarities between tonic immobility and stillness reactions in women victims of rape – “rape-induced paralysis”.

Galliano et al. (1993) conducted the first systematic study on tonic immobility in female rape survivors. More recent studies assessed this phenomenon through retrospective reports of the traumatic events in a more systematic way using psychometric instruments in female victims of sexual assault (Bovin et al., 2008; Fusé et al., 2007; Heidt et al., 2005; Humphreys et al., 2010; TeBockhorst et al., 2015). Other studies expanded the scope to other traumatic events and to men as well as women in different convenience samples: students (Abrams et al., 2009; Bados et al., 2008; Portugal et al., 2012), police officers (Maia et al., 2015) and PTSD patients (Fiszman et al., 2008; Lima et al., 2010; Rocha-Rego et al., 2009).

Recently, peritraumatic tonic immobility was described in a large representative sample of the general population through retrospective reports (Kalaf et al., 2015). The authors observed that quantified scores of tonic immobility were more than double for the subsample who met the criteria for PTSD. This is not surprising given that the diagnostic criteria for PTSD include exposure to actual or threatened death, serious injury or sexual violation (American Psychiatric Association, 2013), which are also triggers for tonic immobility.

In a series of studies examining PTSD patients exposed to gun-related violence from our university outpatient clinic, retrospective reports of peritraumatic tonic immobility were observed to correlate with the severity of PTSD symptoms and refractoriness to pharmacological treatment (Fiszman et al., 2008; Lima et al., 2010; Rocha-Rego et al., 2009).

2.3.2. *Biological assessment and implications for PTSD*

The first human study to successfully report biological evidence for tonic immobility was performed in our laboratory setting employing stabilometry recordings (Volchan et al., 2011). This study was conducted with PTSD patients from the university outpatient clinic.

To simulate exposure to life-threatening events in the lab, PTSD patients and trauma-exposed participants without PTSD passively listened to the script of their personal violence-related trauma.[2] Participants stood upright on the force platform, had electrocardiogram electrodes attached and wore earphones. Immediately after the recording session, participants rated the script-induced tonic immobility through a specific questionnaire. Stabilometry results from Volchan et al. (2011) revealed that participants who rated the highest scores of tonic immobility after listening to the personal trauma-script presented the lowest amplitudes of body sway. Furthermore, those participants also exhibited robust tachycardia and very low heart rate variability after listening to the personal trauma-script. It is worth noting that among the PTSD patients, 40% had very high scores of tonic immobility after listening to the script, while less than 7% of trauma-exposed participants without PTSD scored above the median value of tonic immobility questionnaire (Franklin, 2010). Not unexpectedly, the biological indicators of tonic immobility in the laboratory setting were presented expressly by the PTSD patients, who are more susceptible to re-experiencing the traumatic event, even in an otherwise safe environment.

In summary, the study by Volchan et al. (2011) revealed that an important proportion of PTSD patients, triggered by listening to their personal violence-related trauma script, reacted with sustained tachycardia accompanied by reduced heart rate variability and reduced body sway; which, together with the questionnaire ratings, characterized tonic immobility in humans.

These results suggest that under external and/or internal cues, in daily-life a significant proportion of PTSD patients probably present repeated episodes of tonic immobility-like reactions. This can have harmful effects. For instance, prolonged reduced heart rate variability has been associated with immune dysfunction, inflammation, cardiovascular disease, and mortality (Kemp and Quintana, 2013). In fact, Ratner (1967) had already observed in experimental animals that repeated inductions of tonic immobility potentiate this reaction and have harmful long-term consequences, which are sometimes lethal (Liberson et al., 1961). Indeed, PTSD patients reporting peritraumatic tonic immobility from violence-related traumatic event were found to be the most severely affected

[2] This is not the same as the “personal trauma script-driven imagery protocol” (see Lang et al., 1980; Pitman, 1987) in which participants are instructed to mentally relive the event as vividly as possible during and after listening to the script. In the paradigm that we apply, there is no such instruction and participants passively listen to the scripts. We showed (Norte et al., 2013) that PTSD patients robustly increased the heart rate when passively listening to their personal trauma script, and had sustained or even augmented heart rates after listening to the script. Furthermore, sustained tachycardia was correlated with re-experiencing symptoms. On the other hand, participants without PTSD slightly increased the heart rate during listening to the script and returned to basal level thereafter.

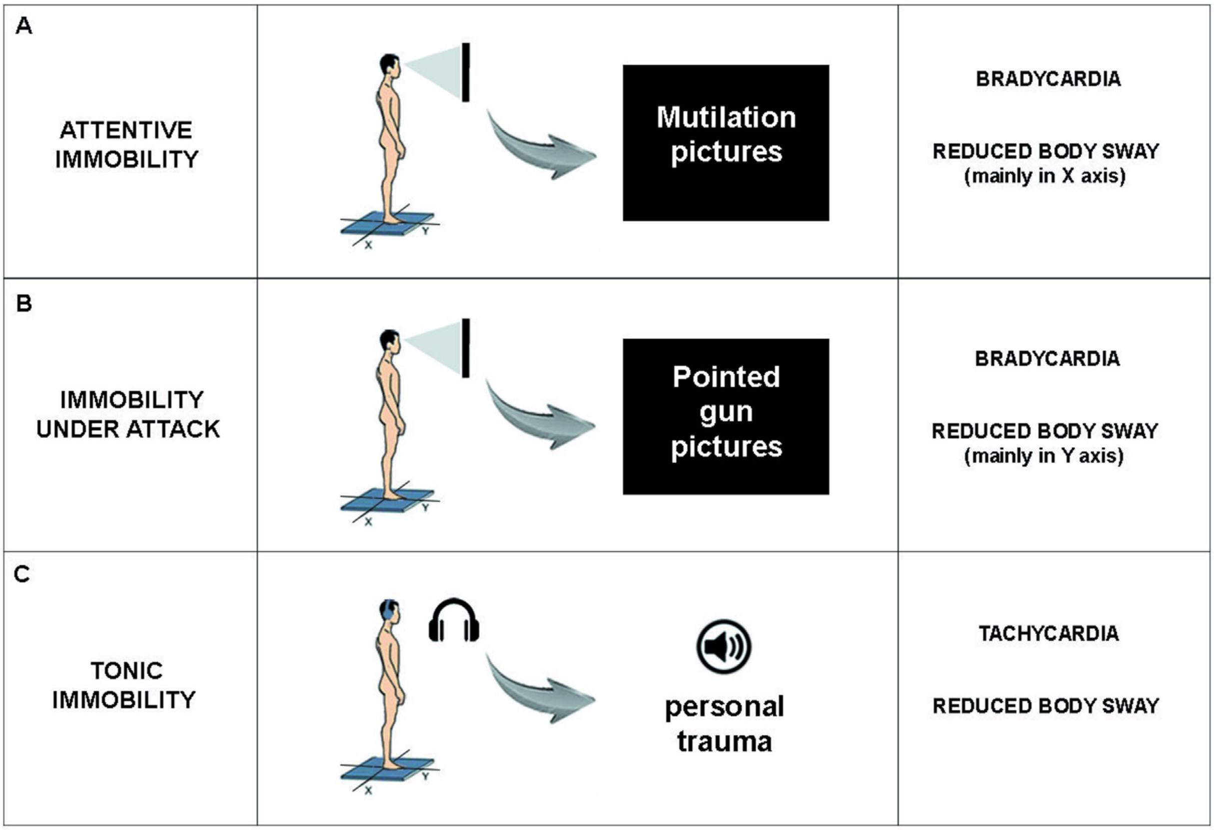

Fig. 4. Immobility defensive reactions in humans- schematic representations of experimental paradigms. (A) Attentive immobility: pictures of mutilation (potential threat) presented on a screen evoke bradycardia and reduced area of body sway – mainly in the lateral–lateral (X) axis. (B) Immobility under attack: pictures of a pointed gun directed at the participant (attack with less possibility of escape) presented on a screen evoke bradycardia and a reduced area of body sway – mainly in the anterior-posterior (Y) axis. (C) Tonic immobility: script of a personal violence trauma (life at risk) listened to through earphones evokes tachycardia and a reduced area of body sway.

(Fiszman et al., 2008; Lima et al., 2010; Rocha-Rego et al., 2009). Repeated episodes of tonic immobility may underpin the severity of the disorder in these patients by rendering them more susceptible to the known hazardous effects of repeated activation of stress mediators on dysregulation of brain and body allostasis (Kario et al., 2003; McEwen and Gianaros, 2010).

Predispositions to react with tonic immobility may be a specific characteristic of some individuals. As discussed by Korte et al. (2005), within-species differences in typical behavioral defensive strategies (supported by particular physiological, neurobiological and neuroendocrinological underpinnings) are evolutionary adaptive. In the face of changes in the surrounding environment, a balance between different traits can be advantageous for a species' survival. However, for a given individual, his/her defensive trait can sometimes be maladaptive. This may have therapeutic implications for those PTSD patients who are prone to tonic immobility reaction.

The pharmacological treatment of choice for PTSD patients is the antidepressants known as selective serotonin reuptake inhibitors (SSRIs). As mentioned before, it has been found that PTSD patients who experienced the highest levels of peritraumatic tonic immobility, were the least responsive to PTSD pharmacological treatment (Fiszman et al., 2008; Lima et al., 2010), raising the need for alternative pharmacological agents. In fact, there is evidence that a neglected class of medications in the treatment of SSRI-resistant PTSD – namely dopaminergic agonists – should receive more attention from researchers and clinicians (Berger et al., 2009; Houlihan, 2010; Naylor et al., 2015). An increased focus on identifying the occurrence of peritraumatic tonic immobility may open the field for the use of more specific pharmacological agents in PTSD.

2.3.3. The benefits of increased knowledge

The occurrence of tonic immobility in humans still remains largely unrecognized. This automatic and involuntary reaction under extreme life threatening contexts may elicit the feeling of terror of being immobilized, adding to the fear evoked by the traumatic event itself (Volchan et al., 2011). Additionally, victims often feel guilty and ashamed by not having been able to react, and sometimes not even scream, particularly victims of sexual abuse (Marx et al., 2008). Professionals like rescuers, police and soldiers may be stigmatized if they undergo tonic immobility when enrolled in a mission to save and protect other people (Maia et al., 2015). Thus, it is essential that steps are taken to alleviate the entrapment symptoms, guilt and prejudice found in the aftermath of tonic immobility, and that information about this involuntary reaction is more widely disseminated to health professionals and the general public.

3. Defensive reactions and the inverted U-shape profile

The present review focused on the human defensive cascade – more precisely on immobility reactions to violence-related threats of increasing intensity. We highlighted studies on immobility reactions to danger cues related to human co-specific violence threats, not tackling the context of predator attacks. Interestingly, studies in rodents have shown that although different neural circuits are involved when animals face social (co-specific) versus predator threats, behaviorally the immobility reactions were shown to be very similar (Silva et al., 2013).

In stabilometry studies by Azevedo et al. (2005) and Facchinetti et al. (2006), pictures of mutilated human bodies, a cue for potential

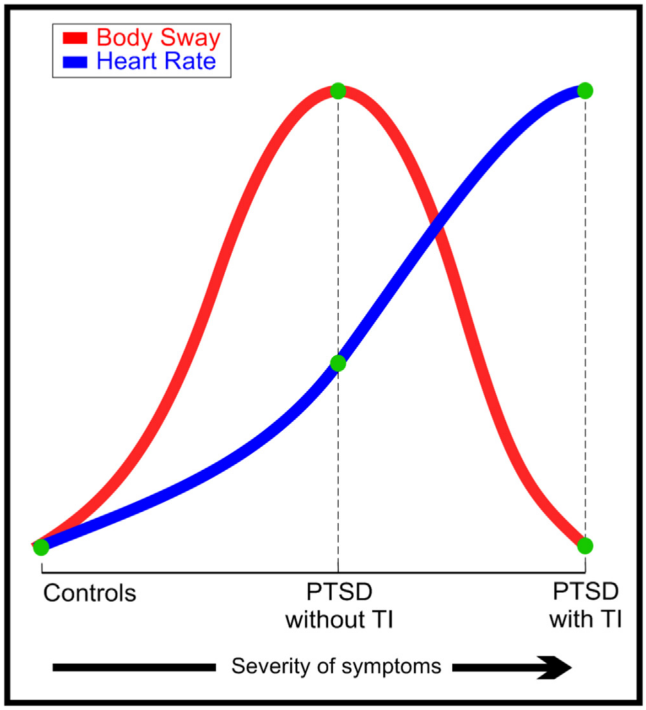

Fig. 5. Schematic representations of body sway area (red) and heart rate (blue) values after passive listening to a personal trauma script (based on Volchan et al., 2011). Controls: violence-exposed participants without PTSD. PTSD without tonic immobility (TI): violence-exposed patients diagnosed with PTSD, not reporting tonic immobility after listening to their personal trauma script. PTSD with tonic immobility (TI): violence-exposed patients diagnosed with PTSD, reporting tonic immobility after listening to their personal trauma script. Note that as the severity of symptoms increases, the profile of the area of body sway across the participants presents an inverted U-shape. In this paradigm, heart rate increases steadily. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

threat, have been shown to induce attentive immobility characterized by a reduction in body sway, mainly in the lateral–lateral axis, and bradycardia (Fig. 4A). Acute threat cued by pictures of a gun directed away from the participant evoked increased body sway, compatible with a predisposition to active escape. When the pictures portrayed a gun directed at the participant, evaluated as more threatening, closer and with less chance of escape; there was a reduction in anterior-posterior body sway and bradycardia; characterizing immobility under attack (Bastos et al., 2016) (Fig. 4B). Overwhelming threat, cued by the audio-play of the personal trauma script, especially in PTSD patients, can lead to the most extreme defensive reaction – tonic immobility, characterized by reduced body sway, robust tachycardia and reduced heart rate variability (Volchan et al., 2011) (Fig. 4C).

The presence of points of disjunction and non-linear functions, like inverted U-shape responsivity curves in studies of stress and mental disorders has been recently highlighted (e.g. Cuthbert (2014); Sapolsky (2015)). It is important to have in mind that an inverted U-shaped profile might be observed when analyzing a parameter associated with threat intensity or symptoms severity. This finding is consistent with the possibility of more than one dimension underlying the responsivity curve, as we discuss below in connection with defensive reactivity.

For instance, the response profile to pictures representing increasing danger: from potential (mutilation), to more threatening but escapable (gun pointed away), to even more threatening but less escapable (gun pointed toward) contexts; led to an inverted U-shaped responsiveness profile characterized by "reduced-increased-reduced" body sway (and to some extent heart rate). That is, a gun pointing toward (compared to pointing away) additionally to being more threatening, is more unescapable, bringing into play an adaptive switch to immobility, instead of continually increasing "mobility".

An inverted U-shaped profile was also found when the postural reactions, after passively listening to their personal trauma script, were compared among participants with increasing severity PTSD symptoms (Fig. 5). Almost no modulation was shown by participants without PTSD (controls); an increased area of body sway was presented by participants with PTSD reporting no tonic immobility; and a lower area of body sway was presented by participants with PTSD reporting tonic immobility. In this case, the analysis of another physiological parameter – heart rate – revealed a seemingly linear increasing trend across these three groups of participants (see Fig. 5).

Another group of researchers (McTeague et al., 2010), tested heart rate reactivity using the personal threat imagery paradigm in three groups of participants with increasing symptom severity: controls, single-trauma PTSD patients and multiple-trauma PTSD patients. Body sway and tonic immobility were not assessed. They found that heart reactivity increased from controls to single-trauma PTSD patients, and fell to control levels in the more severely affected PTSD patients with multiple trauma history, resembling an inverted U-shaped profile.

Another study called attention to an inverted U-shape in their proposal of different stages of defensive reactivity in PTSD patients (Schauer and Elbert, 2010 – Fig. 1, p. 111). In their framework, they hypothesized that in response to a traumatic event, some individuals would present a fight/flight reaction, others would present tonic immobility with intense tachycardia, and still others, especially those individuals with history of multiple traumas, would present a "shutdown" effect and faint (bradycardia and hypotension).

In conclusion, it is essential to have in mind the inverted U framework when analyzing different parameters and across different subjects.

4. Conclusions

The present mini-review synthesized recent advances regarding immobility reactions of the human defensive cascade that seem to have parallels with those proposed for non-human species, bridging the gap between them.

In line with the Research Domain Criteria (RDoC) project (NIMH, 2016), the progresses in basic research to objectively monitor motor defensive reactions under threat can help to develop a dimensional trans-diagnostic approach to PTSD, potentially leading to new avenues of prevention and treatment.

Funding acknowledgements

This work was supported by National Council for Scientific and Technological Development (CNPq), Carlos Chagas Filho Foundation of Research Support in Rio de Janeiro (FAPERJ), and Coordination for the Improvement of Higher Education Personnel (CAPES).

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