Jos F. Brosschot

Ever at the ready for events that never happen

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Inaugural speech by

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Dedicated to Holger Ursin († 13-08-2016)

Sir Rector Magnificus
Ladies and gentlemen officers of the Foundation for Research into Psychosocial Stress and of the curatorium of this Chair
Dear ladies en gentlemen students
Beloved friends and family
Much esteemed audience

In stead of the pain that is here
It is the suffering we fear
For far more events
Than Fate ever presents
We are at the ready for ever
For all that happens, never

(inspired by well known Dutch poem by Nicholaas Beets , 1814-1903)

Introduction: long and short stress responses

One particular day back in the early 90s when I was picking up my daughter Tara from nursery school I was approached by the nursery teachers who regarded me with a mixture of mild accusation yet slight amusement. The reason? They had asked the children that day what kind of work their parents did, and Tara had offered the following; "My dad is a doctor and he makes people... angry." I had some explaining to do. The short explanation is that we were deliberately making test subjects angry and therefore stressed in order to increase their blood pressure and so be able to examine it.
The longer version of this explanation I am going to give to you today.

Psychosocial stress, which from now on I will be referring to as just 'stress', is a killer. It has even been classed as a worldwide epidemic by The World Health Organisation and according to different scientific sources, half of sick days are taken off due to stress and around two thirds of visits to the doctor are stress related. If we look at cardiovascular disorders mostly studies in this respect - , 25% of the most stressed people are twice as likely to suffer a heart attack. These risks are comparable or even higher than those of the more traditional risk factors associated with heart disease like smoking and obesity[1-4]. High work stress increases your chances of developing cardiovascular disease by four, whereas caring for a partner with Alzheimer doubles that chance. Being in a difficult marriage can lead to a three times higher chance of developing heart problems, even after, excuse the pun, an already broken heart. Long-term anxiety disorders are associated with a 2 to 7 increased chance of cardiovascular disease. I could go on, also with examples for other diseases[5-15].

Let us go back to the anger experiment. During my time working with the University of Amsterdam, and supported by the Royal Netherlands Academy of Arts and Sciences (KNAW), I angered test subjects not only to increase their blood pressure but more so in order to study what determined how long this blood pressure stayed high[16-19]. Because it is

precisely *prolonged*, or even *chronic*, stress responses that ultimately damage our health[20-25]. Zebras do not develop gastric ulcers because they do not suffer from chronic stress according to the stress scientist Robert Sapolsky[26] – zebras that is, and all other wild animals. Chronic stress seems to be a human invention.

True chronic stress responses are *daily* stress responses. They are continuous or at the very least last many hours at a time for many months or even years. Short-term stress responses are virtually harmless; being worried for a while, being scared, feeling disappointed, or just being on edge for a short amount of time – these cause a reaction in the body where blood pressure increases and more adrenaline, ACTH and cortisol hormones are released into the blood: A completely natural and healthy bodily reaction. A short-term stress response *can* be fatal for people who are already physically fragile (e.g. through having a heart condition) if coupled with a very strong emotion. Short but extreme stress responses to traumatic events can also lead to long-term health problems, but on the whole, short-term stress responses are not dangerous. On the contrary in fact, they are completely natural responses to a threat. In the past we would be dealing with bears, tigers or enemy tribes – these days it can range from things like receiving an insult or being involved in an argument, losing your wallet or the train doors closing right in front of your nose, having a flat tyre or having facebook-stress: the fear of missing out (FOMO! do you already suffer from it?)

Since Walter Cannon's work around 100 years ago this response in humans and animals has been called the fight-or-flight response, the biological part of which is evolutionary ancient. The importance of our evolutionary background cannot be emphasised enough here. It probably comes as no surprise to you that we humans share 90% of our genes with chimpanzees. But did you know we share 85% of our genes with cows? And 73% with the zebrafish? Even 65% with chickens... and these genes determine for best part the same stress responses. We share almost 40% of our genes with parasitic worms, and still a *quarter* with *grapes*[27]. Something to think about at the reception later when you have your glass of wine! These too are sort of family.

We thus share that fight-or-flight stress response with by far most animals: Chickens, apes, salmon, they all show stress responses similar to those of humans. Even oysters show an increase in the hormones ACTH and noradrenaline when they are stressed - in this case they were exposed to prolonged shaking[28]. A short-term stress response has always been very useful.

Human stress: long-term preparation with no action

A fight-or-flight response with its increased heart rate and blood pressure etc. results in what seems rather similar to the physical effort response[29], which is what you get when you walk up flights of stairs or go running for example. Your heart reacts to an average stressor, e.g. an argument, the same way as it would if you quickly walked the stairs to the top of this building. There is just one difference: during a stressor, like an argument, we humans only *prepare* ourselves for fighting or fleeing rather than raising a fist or legging it immediately. Our heartrate increases nevertheless, just like for example an athlete's heart rate does before a 100m sprint, which incidentally almost doubles, and what difference is there really between a

100m sprint and running away from a tiger?

Even a brief *preparation* for fighting or fleeing is still not harmful. A little stress can actually be a good thing for all kinds of performances like for example having an interview or giving a formal speech for an oration. This is often called 'eustress', or good stress. And yes I must say I have definitely enjoyed some eustress these past few weeks... As long as the body is not set to this alerted state for too long or too often, because as was said before, prolonged stress responses are potentially unhealthy.

Here is the interesting thing. Most stressful events, i.e. stressors, do not last long at all. An unpleasant comment at work happens in a second, or a few minutes bickering with a partner before you go to work is over quickly. A dreaded interview rarely lasts more than an hour or so. The daily encounter with an intimidating boss or colleague or receiving your tax assessment: these are all extremely brief stressors. *Too* brief in fact to explain the prolonged unhealthy stress response. So what *does* explain the prolonged stress response? My colleagues and I have spent the last 15 years creating three hypothetical explanations for precisely this, all of which I will be laying out for you this afternoon.

In short, the first hypothesis concerns the endless worrying and brooding that takes place between stressful events, call it negative rumination. This is something that has been studied extensively by us and by others. The second hypothesis concerns unconscious stress which forms part of our current ongoing research. And the third, the third hypothesis I will reveal to you at the end of my speech as this one still finds itself in the rather more speculative corner.

First let us return briefly to that strong stress response called anger.

It's all in the mind

It is not such an easy thing to make people angry all the while keeping within the ethical norms of scientific research. One thing we did do was letting the test subject attempt to solve a difficult puzzle while constantly pestering him or her with snide remarks such as *"oh, just give up, this isn't working"*. Or my favourite, *"hold your arm still, we're trying to measure your blood pressure!"* This did not work at all, especially as the students conducting the experiment were far too friendly. Could we have expected anything less from psychology students?! They much prefer helping people and making them happy than trying to anger them. When it finally worked with one test subject they got to angry they complained at the faculty and not long after this an ethical committee was established in the psychology department in Amsterdam.

In the anger research done by us and by others[16-19] it was noted time and time again that test subjects' blood pressure would return to normal quicker if the person being tested could do something nasty back to the one who had angered them. This included giving small electric shocks or dismissing that person on a performance evaluation form. Venting frustrations on someone or something *else* does not work: throwing bottles against a wall or slamming a fist into a pillow is fruitless. Frustrations, it seems, need to be dealt with at their core: revenge must be taken on the one causing the frustration. Interestingly, it is not even necessary to perform the revenge or retaliation acts as it were: as long as the *option is there*., the blood pressure will quickly return to normal. It is *all in the mind*[16-19].

Angry rumination

We were however interested in the issue what kept blood pressure so high without the opportunity for retaliation, an opportunity which of course we do not normally have. Was it normal for it to stay so high? We compared the effect of angering subjects with physical exercise. In this case cycling on a stationary bicycle. We did this for the same duration it took to get angry and we made sure the blood pressure increased to the same level. The latter returned to normal much quicker from the cycling than it did after the test subject was angered. In fact it was often still high even when the test subject admitted to no longer being angry. Why? What was going on?

Light was thrown in the issue from research done by a colleague of ours in New York, Bill Gerin. Bill also angered his test subjects, but he then did something else: he distracted half of them with busy colourful posters and other eye-catching objects. This group's blood pressure lowered significantly quicker than that of the not-distracted group – so, distraction also worked. The not-distracted group's blood pressure stayed high for a longer period of time, but not because the test subjects were still angry: because they continued to *ruminate* angrily[30-32]. While Bill limited this idea to *anger* and blood pressure *recovery*, Julian Thayer and I quickly saw the potential in this idea. We convinced Bill that this angry rumination not only delays the recovery from a stress response but can also actually cause stress responses *long before* the stressor even takes place, due to our *anticipation* of this stressor, the fact that we are ruminating about it before it happens. We also believed that stress responses could arise out of the blue as it were, without the presence of stressors, every time we would worry about a given stressor in our life. So not only could *recovery* and *anticipatory* reactions be explained by this rumination but also all stress reactions lacking an immediate stressor. Voila, we had the explanation for prolonged stress responses. We coined this negative rumination and worrying as perseverative cognition, from which the *perseverative cognition hypothesis* was born[33,34]. This brings me to the first hypothesis.

Perseverative cognition

Perseverative cognition is the "constant (*perseverative*) thinking (cognition) about negative events in the past or in the future". Officially *'the cognitive activation of representations of stressors'*. The wonderful thing about this is that it is a purely human stress theory. Animals do not spend time worrying about things, or so we presume: it is only us humans that possess the parts of the brain which have the capacity to create representations of events in the past, i.e. memories, and representations of events that might happen in the future. This for one has brought with it an enormous evolutionary advantage for us, for we were very simply better able to learn from the past and make plans for the future. But the drawback of all that capacity to think and ponder about the past and the future is that it can often give rise to anxious worrying. And more often than not this worry concerns things that do not even happen.

Our bodies thus react to stressful events that do not take place...

Think about this for a second...if you wish.

Meanwhile we found it strange that in over 60 years of stress research so little had been done in regard to the causes of prolonged stress responses. This is most probably because a vast deal of research is based on experiments concerning animals and as we know, animals do not ruminate. Even Talking Heads sang back in 1979: 'Animals don't worry'. This is the reason why chronic stress is above all a human invention.

Since the publication of this perseverative cognition hypothesis with Bill Gerin and Julian Thayer, there has been a lot of international research into the field. My research group showed in the lab as well as in daily life, that negative rumination increases cardiac activity. In one of those studies student Eduard van Dijk and I gave 80 volunteers a small box to carry with them for a day which measured their heart activity. We asked them to keep a diary noting their ruminations and worries throughout the day: the stressors they experienced. Heart activity indeed increased thanks to worry. It was not possible to link this increased heart activity to negative emotions nor to smoking, drinking coffee or physical exercise – it linked overwhelmingly to rumination. Doctoral candidate Suzanne Pieper, financed by The Netherlands Organisation for Scientific Research (NWO) later reproduced these results[35,36].

Other research groups have come to similar conclusions. Take the research done by Cristina Ottaviani from Rome, who is present here today. Together with us she has shown in a recent meta-analysis that all the research collectively points to the conclusion that perseverative cognition leads to increased physiological activity, and not only of the cardiovascular system but also of our hormone system[37]. Salient detail was that the journal that published this meta-analysis, Psychological Bulletin, had previously rejected the original article on the perseverative cognition hypothesis exactly 10 years previously. It was considered then to be 'too speculative'. We secretly find the recent publication a satisfying reparation.

In the meantime various studies have shown that excessive worrying can increase the risk of illness in the long term[38-49].

Worry interventions

It is not easy to stop worrying. In a well-known cartoon a psychiatrist says to a patient: "you worry too much... it's a waste of time", to what the patient replies, "well it works for me... 95% of the things I worry about never happen". Current 'anti-worrying' methods are not in optimal working order so we are currently trying two new methods ourselves. Doctoral candidate Anke Versluis is attempting to lessen the worry and lower the heart activity of people who suffer from high work stress unconscious. She does this by sending mindfulness-type tasks to their smartphones multiple times a day. Andreas Burger, financed by means of a VENI grant to Bart Verkuil, is quite revolutionary attempting to break the vicious circle of worry, the cognitive perseveration, through subtly influencing the brain by stimulating a nerve end in the ear[50]. The results of these studies are yet to be revealed.

Why perseverative cognition?

Perseverative cognition. Why choose such a difficult word? Why choose a new word altogether?

Once when my son Felix was around three years old he was sitting in the car quietly – something that incidentally was quite a rare occurrence and after a long pause he asked me "Daddy, does everything have a name?"
I must have given an answer along the lines of, "No, not everything has a name. There are many things that we don't know yet so we'll need lots of new names."

Is perseverative cognition a name we need? Why not just 'worrying' or 'rumination'? At first I could not even pronounce it in English, which incidentally is quite ironic for something you have thought of yourself.
The reason for choosing such an umbrella term is that there are many more stress related thought activities than just worrying. Pondering, brooding, agonizing over something, ruminating, or the great words 'peinzen' and 'piekeren' in Dutch, all fall under the 'perseverative cognition' category. People think long and hard about various problems without necessarily 'worrying' about them but it can still have physiological effects, as was discovered by Bart Verkuil's experiment in our laboratory[51].

But there is more. Our mind likes to wander and we spend large parts of the day daydreaming. The psychologists Killingsworth and Gilbert discovered[52] that we in fact spend half the time daydreaming, of which around 40% is about positive things and the rest about neutral or negative things. Surprisingly enough, daydreaming about positive things did *not* make their test subjects any happier, while daydreaming about negative *as well as* neutral things made people *less* happy. So daydreaming apparently makes you unhappy. They did not call their Science article 'A wandering mind is an unhappy mind' for no reason. Over the years Cristina Ottaviani has convincingly shown that part of daydreaming is formed of perseverative cognition, and that this part goes hand in hand with a stronger and unhealthier bodily activity[53-57].

Not all prolonged stress responses are explained

Can perseverative cognition explain all prolonged stress responses? We started to realise in the last seven years that there is more to it.
In the first instance we discovered that after a day of worrying heart activity also remained high at night during sleep[35]. And most definitely not only during the deep sleep period in the latter part of the night. This was later also discovered by researchers in the US and Japan[58-60].
Our colleague Tica Hall had previously also found a strong indication of this in her sleep laboratory in Pittsburgh[61]. She had a group of students sleep in her laboratory of which half were told before they went to sleep they had to get up at 8am to deliver a speech to an audience. The other half were told nothing. In the latter group heart activity decreased as per normal during the night. But in the first group heart activity remained high and did so for the whole duration of the night – not because they slept any worse, which of course was to be expected slightly, but because apparently their brains and bodies were constantly engaged with stressing about the looming speech.

Why is this so important? It is important because we spend around a third of our lives asleep, and if the prolonged stress response stays 'on' even during the night when we are sleeping it means a very serious prolonged stress response: we are not only alert throughout the day, but throughout the night too! My mother is 90 years old. She has spent 30 years of her life asleep

(minus the sleepless nights that my brothers and I gave her!) If she had had high blood pressure throughout those 30 years she would not be sitting here in front of me today.

Another reason why this is so important is that a sleeping human cannot consciously be worrying. The obvious question here is how is it possible to have increased heart activity from the events of the day before, when you are asleep and thus cannot consciously be worrying? Do stressful feelings and thoughts continue into the night at a unconscious level? There is indeed some proof for this in neurobiological sleep research [62-64].

It also raised another question. If unconscious stress-related cognition (unconscious stress) is active at night and can lead to physiological effects, could this possibly happen during the day too? This brings me to the second hypothesis: the unconscious stress hypothesis[65,66].

Unconscious stress

Suzanne Pieper measured the heart activity of over 100 teachers in their day to day life and asked them via palmtop computers if they had been worrying/ruminating. As expected rumination caused elevated heart activity, but heart activity remained high for an average of two hours after the test subjects had stopped worrying! This continuation could not be explained by stressors, emotions, physical movement, smoking or anything else. It seemed that the test subjects continued to worry without even knowing it themselves! We consulted available literature to see if this could be possible and if we could find any further leads into the physiological effects of unconscious stress. We had positive results in both cases[67].

One person who tested the physiological effects of unconscious stress was Rebecca Levy from Toronto. She wanted to see if it was possible to influence the stress response of older people by subliminally (and thus unconsciously) presenting them with negative words related to growing old i.e. stressful stimuli for older people. Words were used such as: confused, sick, demented, frail. She compared this with positive words such as wise, mature, experienced. Levy discovered that blood pressure indeed increased when test subjects were exposed to the negative words, and that it stayed lower if they had been exposed to the positive words[68].

One of the things we have realised about the brain during the last 20 years is that we are not at all conscious of most of its activity[69-71]. It therefore seemed highly plausible that we are neither conscious of a large part of stress related information in the brain, while they can still have visible physiological effects. This meant we had to expand the perseverative cognition hypothesis.

Our bodies not only react to stressful events that do not take place...but we are not even conscious of them doing so!

Bart Verkuil, Julian Thayer, and I published the new theory about unconscious stress in several articles[65,66] and we have also more recently published some evidence in support. We

have found further evidences of physiological effects of subliminally presented threatening stimuli in other studies, among which doctoral candidate Melanie van der Ploeg's work[72,73].

How do you *measure* unconscious stress in day to day life? How do you measure something in humans that they are not aware of? We are very busy researching this at the moment with the financial support of a TOP grant from the Netherlands Organisation for Health Research and Development (ZonMw). I cannot do justice in my talk today to the theoretical and methodical complexity of our studies but I can report an example from one of our findings. We were able to measure unconscious negative emotion using an ingenious method by Marcus Quirin from Osnabrück University[74], both with Melanie in the Leiden laboratory and doctoral candidate Mirjam Radstaak in Nijmegen. This unconscious negative emotion was associated with slower blood pressure recovery after a stressor.
Research to unconscious stress continues at a slow but steady pace. Dare we say that we had solved the puzzle? That all prolonged stress responses are due to conscious and unconscious stress related cognition but that the latter is not fully measurable? No. I found this explanation unsatisfying and a bit 'too easy'.

Furthermore, chronic stress responses often seem to appear when they are very clearly not caused by *stress*, nor by *unconscious stress*. Take for example loneliness. Loneliness often goes hand in hand with a chronic physiological response that looks very much like a stress response. It also carries increased chances of illness or early death[76-82] and it is something that is seen more and more frequent in our individualistic and greying society. So what causes the stress response in loneliness? In itself it is not a threat, it is not a stressor. It does seem however that those who suffer from loneliness are lacking in something: a warm, supportive, safe social network – something which is so important for social animals such as humans; call it love for a better word. But why would one show signs of a stress response, even a chronic stress response, with the absence of love, if there is no sign whatsoever of a stressor? This, ladies and gentlemen, brings me to my third and final hypothetical explanation: The role of safely and the default stress response when safety is not present[83,84].

Not stress but safety? The default stress response

When a starling does not have access to water to clean its wings it becomes more vigilant and more aware of danger. The starling who cannot wash its wings, even when they are not necessarily dirty, seems therefore to show a stronger stress response, while there is no sign of an actual stressor[85]. A similar thing happens with zebra finches[86] who show a higher level of the stress hormone corticosterone if they have not been able to bathe for a while. (Maybe zebra *finches do* get gastric ulcers!) This in truth should come as no surprise for without water to wash one's wings, fleeing when danger approaches is a far less effective operation – one cannot take flight as quickly with dirty wings. Being more alert when there are no washing opportunities is therefore highly beneficial for survival. The more vigilant birds were the ones who could pass on their genes.
Another example. A squid who has lost part of one of its eight legs sees a small neutral object (e.g. a wire) as threatening. When presented with such an object it retreats quicker, hides, flees quicker or squirts a cloud of ink quicker than normal[87]. So a mildly handicapped squid is

also much more alert even when there is no immediate threat.

Stress responses without stress

How can the lack of washing facilities or missing part of one of your eight legs lead to seeing threats when there are none? Try to put yourself in their "shoes"!
These are most certainly not isolated cases. Farmers could tell you that dirty and badly cared for animals look more stressed, and it has emerged in many studies that animals do not need a direct threat (a stressor) to become stressed. All that is often needed is the presence of another strange animal or human, an owner's unusual behaviour, a clean litter box or nowhere to hide yourself, for stress levels to increase[88-95].

So stress responses when there are no direct threats nor specific obvious dangers is something very common. Why is this so?

Default stress response

The answer is actually very simple, but nevertheless surprising. A stress response does not need a stressor at all, it is simply always 'on', and it stays on as long as there is no obvious safety. It turns 'off' if the situation or surroundings are perceived as safe and turns on again if this perceived safety disappears. The stress response is therefore a 'default' response. Default means a preselected condition where there is no other input i.e. no relevant information. The relevant information in regard to a stress response is safety. With no safety signal the stress response stays on: everything falls back to default and is seen as unsafe. The default here is a state of generalised unsafety. It is that simple.

We humans are naturally, by *default*, afraid of the unknown. As we grow up we learn to recognize the safety signals, but from the very beginning we fear without a sign of threat. This is wonderfully portrayed in a Sigmund strip in the Volkskrant newspaper where a patient complains about being 'scared of the unknown' to the doctor. "I don't know," answers the man when doctor Sigmund asks him what exactly he is scared of, "I don't know anything about it..."

Evolution theory and neurobiology

Even so, this idea of a default stress response does sound strange, and what is worse is that this goes in stark contrast to current stress theories. Stress theories speak of a stress response as a *response* to a *stressor* i.e. as a direct response to a threat.
But this idea of a default stress response does correspond to modern evolutionary theoretical insights about stress and anxiety, and more importantly to neurobiological knowledge – the knowledge of how the brain and the nervous system works. The parts of the brain responsible for the stress response, for example the amygdala, are chronically suppressed by the so called prefrontal cortex[96-101]. (This is the part of the brain that lies at the front of the skull just above the eyes). But, as the researchers Steve Maier and colleagues have demonstrated[96-98], this prefrontal suppression only takes place when the brain has perceived safety. If safety is no longer perceived, the pressure is immediately eased, the brake is immediately lifted, the amygdala resumes its activity and the body is instantly ready to flee away or stand and fight. Heart activity increases and blood pressure goes up etc..

The stress response is therefore always set to high alertness. But kept suppressed as long as safety can be perceived and *let go* whenever it is no longer safe. This neurobiological principle is actually very common and is known as the *Hughlings Jackson principle*. Back in 1884 Hughlings Jackson wrote that evolutionary old responses like the stress response are not actually *turned on* or *pushed* into action but rather *let go* or *released*[102]. That release happens much quicker than turning something on or pushing a button so to speak, which is extremely important with such a vital response mechanism.

High alertness and an ultrafast stress response when in unsafe surroundings has enormous survival power. In the wild it is better to play it safe and to sprint away from something ten times too often than once too few. A principle otherwise known as the *better safe than sorry principle* in evolutionary theory. Creatures who waited to see what exact dangers were approaching did not survive and did not reproduce. Those who sprinted- or flew- or swam away at the drop of a hat however continued to thrive[103,104].

GUTS

We have developed the idea that a stress response is a default response that is chronically suppressed if there is no speak of safety into a new theory. We have called this theory the Generalised Unsafety Theory of Stress, otherwise known as GUTS. We – Bart and Julian and I, have recently extensively argued this theory in a number of articles, the latest of which has just been published in the Neurobiology and Biobehavioral Reviews journal.

GUTS takes us to entirely new hypotheses.

The heavier you are the more dangerous your world

There are many bodily conditions in which we see increased physiological activity such as increased heart activity, high blood pressure, and an increase of the so called stress hormones, which look very similar to prolonged stress responses: for example obesity, low aerobic fitness and old age. These conditions also carry significant health risks but they are not often considered to be direct causes of stress responses. We think that people in these conditions are stressed. We think that, irrespective of other biological mechanisms that cause the increase in their physiological activity, that the default stress response in the above physical conditions is not being fully suppressed , because through millions of years of evolution they carry with them a less adequate fight or flight response. They are ‘not optimally resilient’ bodily conditions. We call them *compromised*. An older or less fit body reacts slower to its potentially dangerous surroundings, like the starling or the squid, which means their world is less safe. The heavier or less fit you are the more dangerous your world is. High alertness was therefore key for survival. For millions of years, our world was a predatory and dangerous place to live in, every day could be your last.

Therefore in summary:

Our bodies do not necessarily react to stressful events... but rather, cease reacting when safety is perceived, or in fact, when safety would have been perceived by our ancestors.

Conclusion

Ladies and gentlemen, I am approaching the end of my talk. We have come a long way in stress research in the last century, from when George M. Beard claimed the following about the rise of *Nervousness* (an old term for stress) in 1881;
" The chief and primary cause of ... [the] very rapid increase of nervousness in modern civilization, [is due to (JB)] these five characteristics: steam power, the periodical press, the telegraph, the sciences, and the mental activity of women."

That was 1881. Nowadays we have stressors from wholly new sources, like those I mentioned earlier: work stress, relationship stress, social media stress, FOMO etc. I hope that today I have made clear my belief that there should be less focus on stressors themselves and more emphasis on prolonged stress responses. I have spoken about three mechanisms that cause this unhealthy prolonged stress response in which I plan to further my research: Firstly the already partly proven perseverative cognition, secondly unconscious stress, which we are currently working on, and thirdly the default stress response, for which we are currently developing research ideas. All three are deeply rooted in millions of years of evolution. Despite the fact that the dangers of back then have virtually disappeared, today many of us remain *ever at the ready for events that never happen*.

Acknowledgements

I am very grateful to the Foundation for Research into Psychosocial Stress (SOPS) for establishing this Chair. I am also deeply thankful to the Executive Board and the Faculty Board for the trust shown in me, as I am of course to the Health, Medical, and Neuropsychology unit at the Institute of Psychology.

The longer you hang around in this field of study the longer the list becomes of people you owe your thanks to. I could have easily spent these 45 minutes doing just that. I shall therefore name only those who have had a more direct involvement in the work I have spoken to you about today. First of all I have been benefitted greatly by the thorough work and critical questions and thoughts of the many master students and doctoral candidates who I have had the honour of supervising, and still supervise – a few of whom I have named today. You all thankfully dealt very well with my constant rambling and never ending theoretical explorations! Over time I have had some wonderful colleagues, from whom I have learnt a great deal and a number of whom have become my very close friends. I would like to start with three people in particular who have become my most important theoretical sparring partners over these past years: my good friends Guido Godaert, once my mentor and still my inspirer with his stimulating questions and associations; Julian Thayer with his extensive knowledge and impressive insights; and Bart Verkuil with his supple mind and creative ideas. The 'Science in cars and airports' with Julian and the brainstorming sessions with Bart in the De Jaren restaurant in Amsterdam lie at the base of a lot of the things I have been telling you about today.
A special thanks goes to our foreign colleagues Cristina Ottaviani and Omer van der Bergh who are both here today, also Bill Gerin and especially to our early inspirer, the late Norwegian Hoger Ursin who sadly passed away not long ago at the age of 82. He was one of the few people who *did* take the prolonged stress response seriously from as early as the

1970s, without having the audience he deserved. I dedicate this oration to him.

I have also benefitted greatly from many others including Richard Lane; Winnie Gebhardt, my very first student and now long-standing befriended colleague; Arie Dijkstra, Merel Kindt, Sabine Geurs and Michel Kompier; Miranda Ollf, Paul Schreurs, Gerard van de Willigen, Rudy Ballieux; my Leiden colleagues including Bernet Elzinga, Willem van der Does, Peter Putman and Philip Spinhoven; Stephen Brown, and I would like to specially thank Andrea Evers for her enthusiastic and stimulating leadership.
I would also like to mention Wijo Kop, Ivan Niklicek, the critical minds of Lorenz van Doornen and Ad Vingerhoets, who in the last 15 minutes probably had their own ideas, and not to forget Ad Kaptein and Gerard Kerkhof who took the initial steps to set up this Chair.

Further afield I have always had the warmth, support, inspiration my brothers and my friends, especially how they helped putting things into perspective. One or two of you might think of me as a chatterbox, well you haven't met some of those friends! Without offending all the other chatterboxes, I would like to thank one in particular, namely Toon van der Sandt, who could ever so often turn my still unripe thoughts into entirely unique yet enlightening formulations.

But it all started with my beloved parents who are both present here today, who gave my brothers and I the freedom and support in everything we did. They are a wonderful example of unconditional love. In their eyes their four sons were to pursue what interested them most, whatever that was to be. At a young age I was presented with books about evolution and prehistory that I could hardly take in. But you understand now where it all comes from...

I also want to thank, of course, my life partner Nelleke. Apart from being my beloved for the past 40 years next year, she has been my most important support with her indestructible positive attitude both in private life and in my work, even if the latter was just with a grounding wink. She has never failed to point out how commonplace my greatest revelations were, so in any case my feet were kept on the ground at home. But if she found something truly exciting about my work, that was a sign for me that it could mean something...

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I rest my case.

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