Artículo de Investigación

Classification of the stimuli that elicit the sympathetic skin reflex. Non-physiological, physiological and cognitive and emotional stimuli

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ABSTRACT

Introduction: The sympathetic skin response is generated by a diversity of non-physiological, physiological, cognitive and emotional stimuli. The stimuli that induce the response seem to be disparate and unrelated. We propose a classification of the stimuli that induce the electrodermal response and suggest a common physiological basis underlying the various stimuli. **Subjects and methods:** We studied twenty healthy subjects in whom the sympathetic skin response was induced with: 1) a cough; 2) a sudden blank noise; 3) eye opening; and 4) muscle contraction. The electrodermal response was obtained ten times in each subject with each stimulus. The stimulus was given one minute apart. The respiratory, the acoustic, the eye opening and the muscle contraction stimuli were recorded in the traces of all subjects. We also obtained the response at least three times in each subject during the moment of standing, sighs, sudden inspirations, talking, unexpected tactile stimulation, verbal instructions, mental calculations, and during the cold face test. **Results**: The response was readily obtained with cough, noise, eye opening and muscle contraction in all normal subjects. The amplitude of the response varied from trial to trial and from subject to subject. We did not give repetitive stimulation to habituate the response. Somnolence was the most common cause of an absent response. Sighs were the most common cause of a seemingly spontaneous response. Laughter and mental calculation gave a large and long lasting response. **Discussion:** The proposed classification of the sympathetic skin response in non-physiological, physiological and cognitive and emotional seem to have some heuristic value. The sympathetic skin response seems to be part of a generalized mechanism of arousal and attention in which there is sympathetic activation of the eccrine skin glands of the skin. The sympathetic skin response is a complex response that acquires a physiological meaning when seen as a part of a generalized sympathetic activation. The sympathetic skin response should always be recorded with respiratory movements. Noise, eye opening, muscle contractions, verbal instructions and somnolence are confounding factors that should be monitored.

Key words: Sympathetic skin response, classification, stimuli, respiratory movements, sensory activation.

RESUMEN

Introducción: *La respuesta simpática de la piel es generada por diversos estímulos no fisiológicos, fisiológicos, cognitivos y emocionales. Los estímulos que inducen la respuesta parecen ser dispares y no relacionados. Proponemos una clasificación de los estímulos que inducen la respuesta electrodérmica y sugieren una base fisiológica común subyacente a éstos.* ***Métodos:*** *Se indujo la respuesta simpática cutánea en 20 sujetos sanos con los siguientes estímulos: 1) tos; 2) ruido en blanco repentino; 3) apertura ocular; y 4) contracción muscular. La respuesta electrodérmica se obtuvo 10 veces en cada sujeto con cada estímulo, los estímulos se aplicaron con un minuto de diferencia entre ellos. Se registraron los estímulos respiratorios, acústicos, de apertura ocular y de contracción muscular en los trazos de todos los sujetos. También obtuvimos, al menos tres veces, la respuesta en cada sujeto durante el cambio a bipedestación, suspiros, inspiraciones súbitas, habla, estimulación táctil inesperada, instrucciones verbales, cálculos mentales y durante la prueba de sumergir la cara en agua fría.* ***Resultados:*** *La respuesta se obtuvo fácilmente con tos, ruido, apertura ocular y contracción muscular en todos los sujetos normales. La amplitud de la respuesta varió de ensayo a ensayo y de sujeto a sujeto. No dimos estimulación repetitiva para habituar la respuesta. La somnolencia fue la causa más común de una respuesta ausente. Los suspiros eran la causa más común de una respuesta aparentemente espontánea. La risa y el cálculo mental dieron una respuesta larga y duradera.* ***Discusión:*** *La propuesta de clasificación de la respuesta simpática de la piel por estímulos no fisiológicos, fisiológicos, cognitivos y emocionales parecen tener algún valor heurístico. La respuesta simpática de la piel parece ser parte de un mecanismo generalizado de excitación y atención en el que hay una activación simpática de las glándulas ecrinas de la piel. La respuesta simpática de la piel es una respuesta compleja que adquiere un significado fisiológico cuando se ve como parte de una activación simpática generalizada. La respuesta simpática de la piel siempre debe registrarse con movimientos respiratorios. El ruido, la apertura de los ojos, las contracciones musculares, las instrucciones verbales y la somnolencia son factores de confusión que deben ser monitoreados.*

Palabras clave: *Respuesta simpática de la piel, clasificación, estímulos, movimientos respiratorios, activación sensorial.*

Introduction

Although the sympathetic skin reflex (SSR) in response to an electrical stimulation has been widely used to assess the integrity of the sympathetic outflow to the sudomotor skin glands, it is difficult from the perusal of the current and past literature to know what the range and limits of its clinical usefulness and its physiological meaning are.[1-3] One of the difficulties in the assessment of the SSR may reside in that since its discovery in the late XIX century by Tarchanoff[3] it has been applied to various problems and conditions but it was not was, until recently, thoroughly studied in its physiological mechanisms. Given its variability in latency and amplitude and its tendency to readily habituate some authors are even skeptical that the SSR may be of any clinical use (Low PA, Fealey RD). Others authors have enthusiastically utilized it in the evaluation of peripheral neuropathies, central nervous system diseases and complex regional pain syndromes.[4-8] Despite the discrepancies the majority of the researchers in the field are in agreement in the following facts: 1) the SSR habituates rather rapidly and therefore the electrical stimulus (or any stimulus) should be given at least one minute apart;[1,3] 2) the latency is variable but in the palm of the hands is around 1.5 seconds, whereas in the sole of the feet is around 2 seconds;[3,9] the latency however may be highly variable from person to person; 3) the amplitude of the response varies from trial to trial and from subject to subject and given the variability of amplitudes and latencies, many authors consider that only the presence or absence of the response should be taken into account;[1,2,10] 4) the conduction velocity of the amyelinic C fibers that mediate response is between 1.5 and 2 meters per second;[11] 5) the SSR may be elicited by a variety of stimuli including: electrical stimulation to a mixed or sensory peripheral nerve, transcraneal magnetic stimulation, sudden inspiration and expiration, Valsalva maneuver, sighs, cough, sudden noise, pinching of the skin, changes in temperature, standing, muscle contraction, eye opening, talking and several emotional and cognitive stimuli such as mental calculation and laughter. Most of the stimuli have an arousal or attentional effect;[3,4,12-16] 6) it has become clear that the efferent arm of the reflex is mediated by the sympathetic cholinergic C fibers to the sudomotor glands; the afferent part of the reflex is non-specific and may come from the skin, the auditory system, the respiratory system, some unknown internal signals, the visual system, from cognitive and emotional changes or even without an apparent external or internal stimulus;[3,4] 7) the actual response is generated by the electrical activation of the sudomotor glands and from the surrounding epidermis;[17] 8) it is absent in patients who have had a sympathectomy although in some patients it is only reduced. It may return months or years after the sympathectomy;[1] 9) the SSR appears spontaneously in normal subjects apparently at random;[1] 10) sudomotor activation of the glabrous skin has been related mostly to emotional sweating and less to thermoregulatory sweating;[2] 11) the medial frontal lobes and the parietal lobes have been observed to be co-activated during the SSR;[16] 13) the initial negative phase of the response seems to be related to the electrical activation of the sweat gland whereas the late positive phase to activation of the epidermis. An electrical gradient exists between the palm of the hand, that is electronegative, and the dorsum of the hand, that is electropositive.[17,18]

Some advantages of the SSR should be emphasized: 1) it is easy to obtain; 2) it is not time consuming; 3) it is not invasive; 4) it gives an indication of the integrity of the sympathetic fibers to the sudomotor glands; 5) it is inexpensive and it can be performed in most EMG machines and on analogical and digital polygraphs.[3,4]

What sense can we make of this disparate information? It seems that, given the great variety and apparently unrelated stimuli producers of the response, a classification of the diverse type of stimuli that induce the reflex should be attempted. We divided the stimuli in: 1) non-physiological stimuli, such as electrical and magnetic stimuli; 2) physiological stimuli (respiratory maneuvers, noise, eye opening, unexpected tactile stimulation, cough, muscle contraction, standing, talking, pain, changes in temperature, etc.); 3) emotional and cognitive stimuli (laughter, sighs, crying, anger, anxiety, mental calculation, etcetera) *(Table 1)*.

We decided to put our classification to a test. Our main interest in the study was to evaluate some of the physiological and cognitive putative stimuli and see whether they were effective in producing the response. Most of the stimuli that we used were already reported previously as inducers of the response, although many have not been systematically studied. We decided to give the type of stimuli that could be recorded in the tracing in order to be more clear regarding the onset of the stimulus and have a more quantitative type of stimulus. Several stimuli that induce the response, e.g. mental calculations, verbal instructions, unexpected tactile stimulation, are difficult to quantitate from the stimulus viewpoint and are not useful regarding latency of the response. We found that eye opening, noise,

Table I. Classification of the stimuli that induce a sympathetic skin response.

Non-physiological stimuli	Transcraneal magnetic stimulation, electrical stimulation of a sensory or mixed nerve
Physiological stimuli	Inspiration and expiration, Valsalva maneuver, unexpected noise or tactile stimulation, eye opening, cough, muscle contraction, talking, pain, standing, changes in temperature
Emotional and cognitive stimuli	Sighs, laughter, crying, anger, anxiety, mental calculation, arousal, change of attention

respiratory movements of several types including cough and muscle contraction stimuli could be recorded in the polygraphic tracings. Despite this disadvantage we recorded in several individuals the SSR during the act of standing, unexpected tactile stimulation, sighs, laughter, arousal, mental calculations, cold face test, and during electrical stimulation to the median nerve.

Subjects and methods

We studied twenty normal subjects without a history of peripheral or central nervous system disease who were informed of the non invasive and non painful nature of the tests. All of the subjects, mostly medical students and residents, volunteered for the study and none withdrew from the tests. None of the subjects had anticholinergic or antiadrenergic medications. The age of the subjects varied between 18 and 32 years with a mean age of 24. The studies were performed in the morning after the subject had a light breakfast. The subjects had no coffee and did not smoke before the test. None of the subjects had taken an anticholinergic medication. The temperature of the room was kept at 26 degrees Celsius. The skin temperature of the palm of the hand was maintained between 32 and 36 degrees Celsius. We constantly urged the subjects to be alert and to try not to fall asleep.

The SSR was recorded in the palm of both hands in 15 subjects and in one hand in five subjects. The active electrode was placed in the palm and the reference electrode in the dorsum of the hand. A ground electrode was located at the head of the radius. The L.F. was set at 0.32 Hz and the H.F. at 1,000 Hz. The gain was set at 100 to 1,000 μV per square and the sweep speed from 5 to 30 to mm/s. The skin impedance was kept below 5 Kω. We followed the recommendations of the International Federation of Clinical Neurophysiology for obtaining the SSR.[3]

Stimuli and recording

The subjects were recumbent in a couch in a semidarkened and semisilenced room with their eyes closed and breathing normally. After five minutes of rest the following maneuvers were carried out: 1) sudden cough; thereafter the maneuver was repeated ten consecutive times with an inter-maneuver interval of one minute. 2) After a minute rest from the previous trial the subjects were given a binaural sudden white noise of 250 ms duration with an intensity of 70 decibels AHL (above hearing level); ten acoustic stimuli were given one minute apart. 3) After a minute rest from the previous trial the subjects were asked to open their eyes suddenly after they had their eyes closed; each eye opening one minute apart. 4) The subjects were asked to raise their right leg for 10 seconds ten times, one minute apart.

The respiratory movements were recorded with a neumograph provided with a piezoelectric crystal wrapped around the lower thorax. The respiratory signal was fed into the amplifier, filtered and displayed at a time constant of 1 second and variable sensitivity. We decided to use a cough rather than a sudden inspiration because the onset of the cough could be very clearly registered in most cases and therefore latency could be more easily calculated *(Figure 1)*. The cough signal makes a sharp negative wave in most subjects *(Figure 1)*.

We had previously observed that the SSR is consistently obtained by opening the eyes after they have been shut for more than one minute. We recorded the eye opening by A.C. vertical electro-oculography with a time constant of 1 s. We put two gold disk electrodes: one above the brow and one below the eye. The signal we obtained was of a good quality. The eye opening and closing could be easily discerned in opposite directions and the latency of the SSR was also easily obtained *(Figure 2)*.

The acoustic stimuli consisted in a binaural white noise of 250 ms duration and 70 decibels above hearing level. The signal was fed into the amplifier in order to record the onset of the stimulus and the onset of the SSR. The acoustic signal was given ten times one minute apart to both ears through binaural headphones. The acoustic signal was recorded in an individual channel *(Figure 3)*.

Then we asked the subject to raise the leg for ten seconds ten times one minute apart. The muscle contraction activity was recorded with a surface EMG electrode located over the quadriceps muscle. The EMG signal was filtered but not rectified *(Figure 4)*.

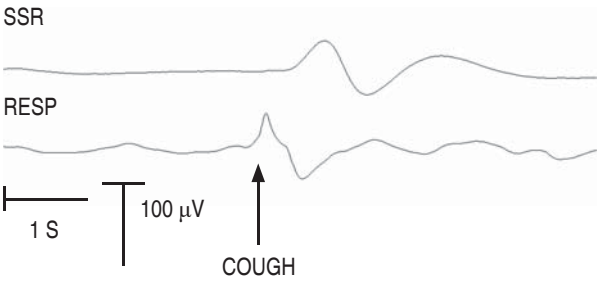

Figure 1. Sympathetic skin response induced by cough. The respiratory signal induced by the cough is seen as a sharp negative potential. The arrow signals the onset of the cough stimulus. The latency of the response is of 1,300 ms measured from the onset of the cough signal to the onset of the SSR. (SSR= sympathetic skin response, RESP= respiratory movement).

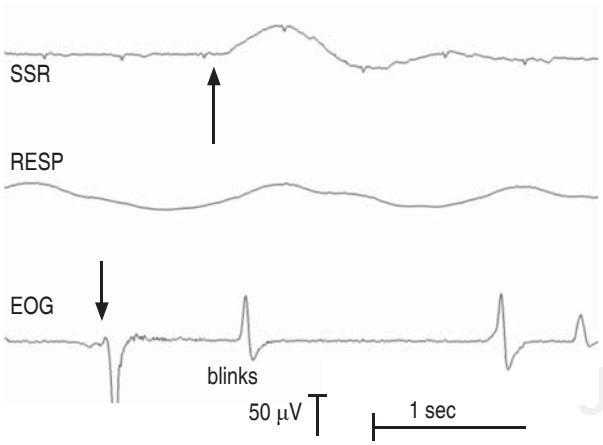

Figure 2. Sympathetic skin response induced by eye opening. The latency was 1,330 ms. (SSR= sympathetic skin response, RESP= respiratory movements, EOG= vertical electro-oculography). Lower arrow-onset of eye opening, upper arrow-onset of sympathetic skin response.

In this study we did not quantify the latencies or the amplitudes of the SSRs and did not intend to measure habituation as our goal was only to see the response to some physiological stimuli that could be recorded and see whether our classification could stand. In a previous study we had recorded the SSR in thirty healthy subjects during sudden deep inspirations and Valsalva maneuvers. We also recorded the response in thirty healthy subjects at the time of standing. We recorded the response in thirty healthy subjects during

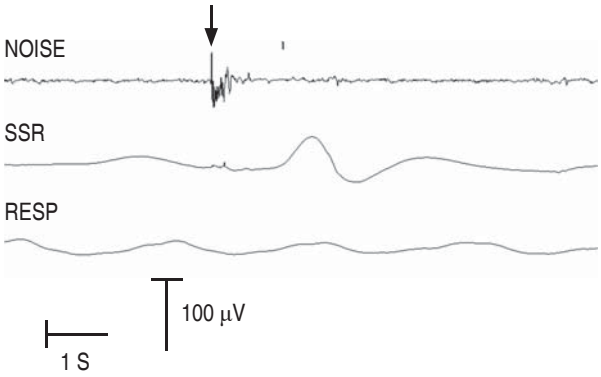

Figure 3. Sympathetic skin response induced by a pulse of blank noise (250 ms duration, 70 decibels AHL). The latency of the response was 1,500 ms. (SSR= sympathetic skin response; RESP= respiratory movement). The arrow signals the onset of the acoustic stimulus. Latency measured from onset of stimulus to onset of response.

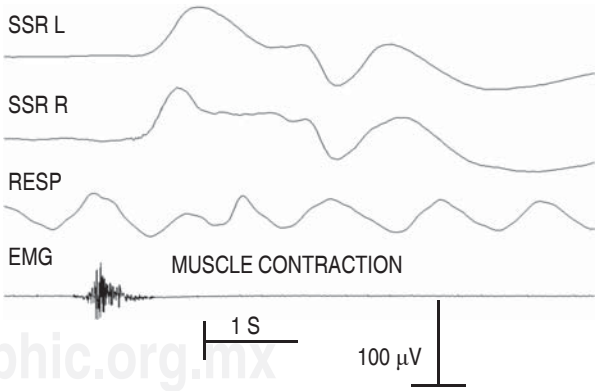

Figure 4. Sympathetic skin response induced by muscle contraction of the quadriceps muscle. The latency of the response was 1,400 ms. (SSR L= sympathetic skin response of the left palm, SSR R= sympathetic skin response of the right palm, RESP= respiratory movment, EMG= surface electromyographic activity of the quadriceps muscle).

sighs, talking, verbal instructions, the performance of mental aritmethics *(Figure 5)*, with electrical stimulation to the median nerve, cold face test, unexpected tactile stimulation and during laughter *(Figure 6)*.

Results

1) Sudden cough invariably induced the response. The signal of the onset of the respiratory movement was clearly recorded as a negative peak. The latency of the response is more easily measured with this maneuver than with a sudden deep inspiration *(Figure 1)*. The amplitudes of the response varied from trial to trial and from subject to subject. We did not observe habituation with this stimulus.

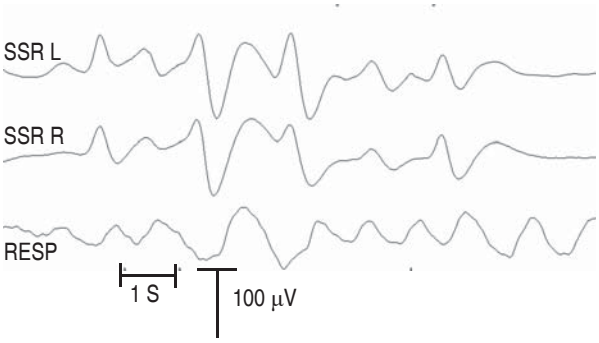

Figure 5. Sympathetic skin response induced by mental calculation. The subject was asked to perform serial seven subtraction. The SSRs are of long duration and variable in shape and amplitude. The respiratory movements were slightly distorted. (SSR L, sympathetic skin response left, SSR R= sympathetic skin response right, RESP= respiratory movements).

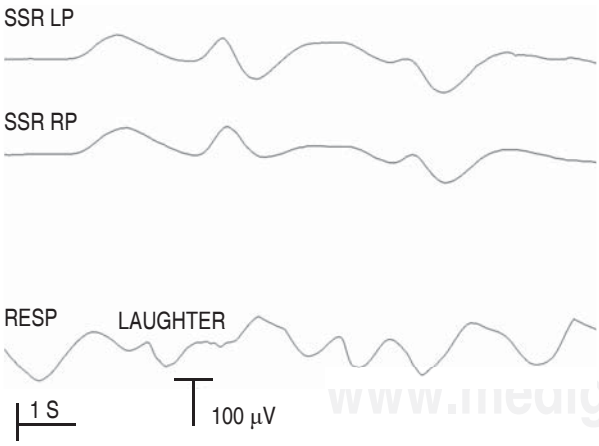

Figure 6. Sympathetic skin response induced by laughter. Notice the distortion of the respiratory movements induced by the laugh. The response is prolonged and has several shapes. (SSR LP= sympathetic skin response left palm, SSR RP= sympathetic skin response right palm, RESP= respiratory movements).

2) The acoustic stimulus induced the response 90 per cent of the trials. The signal of the blank noise was recorded in all subjects. The latency can be measured from the onset of the acoustic stimulus to the onset of the skin response *(Figure 3)*. The amplitudes of the response varied from trial to trial and from subject to subject. When the subjects reported to be somnolent the response was frequently absent. The response was not observed in ten per cent of the subjects even if the acoustic stimulus was given one minute apart.

3) Eye opening induced the response 85 percent of the trials. The signal of the EOG was clearly recorded in the traces and the onset of the eye movement was clearly seen *(Figure 2)*. The eye opening and eye closing are recorded and latencies can be measured from the onset of the movement. The amplitudes of the response varied from trial to trial and from subject to subject. When the subjects reported to be somnolent the response was frequently absent. The response was not observed in fifteen per cent of the subjects even if the stimulus was given one minute apart.

4) Muscle contraction induced the response 90 per cent of the trials. The surface electromyographic signal could be easily recorded in the traces and the onset of the movement clearly seen. The amplitudes of the response varied from trial to trial and from subject to subject. When the subjects reported to be somnolent the response was frequently absent *(Figure 4)*.

5) The skin response could be observed during the recordings at least three times under the following conditions: 1) at the time of standing; 2) sighs; 3) talking; 4) laughter; 5) when given verbal instructions; 6) with unexpected tactile stimulations; 6) unexpected noise; 7) arousals due to any stimuli; and 8) mental calculations. The onset of the stimulus, however, under these conditions is not easily discerned.

6) We also recorded the skin response with an electrical stimulation to the median nerve in four normal subjects.

Discussion

It is clear that non-physiological stimuli such as magnetic or electrical stimulation are rarely found in the life of human beings. The main advantages of these stimuli are that the onset of the stimulus is

clearly observed. The electrical stimulus could also be conceived, however, as a mild painful or tactile stimulation, whereas the magnetic stimulus could be considered as an auditory stimulation.[3]

Physiological stimuli could be further divided in two: 1) those stimuli that are associated with a voluntary or involuntary movement such as standing, muscle contraction, cough, sudden inspiration and even rhythmic breathing, and 2) those stimuli that are associated with a sensory input, either tactile, visual, auditory or even olfactory or gustatory *(Table II)*. We have not used the last two but it is highly likely that they would also induce the electrodermal response. Thermal changes of the skin may be considered, for our purpose, part of a tactile stimulation although there may be a more specific stimulus of a thermoregulatory nature.

What kind of physiological significance these two types of physiological stimuli have? Why the organism produces such a vast amount of electrodermal responses to such miscellaneous and disparate stimuli? The stimuli that are associated with a movement seem to be different to those related to a sensory input. The movements are by definition efferent in nature whereas the sensory stimuli are afferent. The most simple interpretation of the SSR associated to a movement (including respiratory movements, sighs and coughs) is that they represent a co-activation of somatic muscular and autonomic sympathetic impulses. The sympathetic co-activation of the sudomotor glands with a muscle contraction makes sense because in this way the sudomotor glands become ready to dissipate the heat produced by the muscle contraction. It has recently been shown with simultaneous recording of the skin blood flow and electronic measures of the skin temperature that it transiently decreases during an inspiratory gasp.[19] It is possible that some internal signal that induces activation of the sympathetic nervous system, such as transient hypotension, may via the baroreceptor (e.g. during standing or the Valsalva maneuver, cough or a sudden deep breath) induce the activation of the sudomotor glands.

By the same token sympathetic activation of the sudomotor glands during a sensory activation may just be a reflex associated to arousal or attention. We have noticed that simply giving a verbal instruction to do something activates the SSR. This fact has been noted by Kobayashi and his team.[15] The verbal instruction seems to activate attention in addition to the acoustic nature of the stimulus. Therefore we suggest to wait for at least 10 seconds after the verbal instruction is given to perform the maneuver to avoid the contamination of the auditory stimulus from the verbal instruction.

The SSR may also be a response in preparation for action and muscle movement and therefore may just represent a readiness potential activation of the sudomotor glands for dissipating heat. It has been recognized that the activity of the sudomotor glands of the glabrous skin (palms and forehead) is mostly related to emotional activity and perhaps is not as important from the thermoregulatory viewpoint.[2] However, given its association with movement may be significant for both.

It has long been recognized that emotional and cognitive stimuli activate the skin potentials of the palms and soles.[3,13,15] Emotion, such as laughter, is indeed a powerful activation of the SSRs. In long records of the SSR, it is common to see the response during sighs and laughter. Laughter produces a long lasting response or a series of responses. They are easily recognized because they are associated to a distorted respiratory motion *(Figure 6)*. Sighs are the most common cause of apparently spontaneous SSR and are easily recognized in traces where the respiratory motion is recorded. Sighs have an obvious respiratory component but they also have an emotional component.

Table II. Physiological stimuli that induce a sympathetic skin response.

Associated to sensory activation	Noise, eye opening, sudden tactile stimulation, thermal stimulus; olfactory or gustatory stimulus?
Associated to involuntary or voluntary movement	Muscle contraction with or without movement, standing, cough, sneeze, deep breathing, yawning
Cognitive and emotional stimuli associated to movement	Laughter, sighs, crying, talking
Cognitive and emotional stimuli not associated to movement	Mental calculation, verbal instruction

Cognitive activities such as mental calculations are also powerful activators of the sudomotor glands of the glabrous skin *(Figure 5)*. Calculation such as successive subtractios of seven or mental multiplications give a long-lasting electrodermal response. Emotional or cognitive activities may be the most common causes of electrodermal responses not associated with respiratory movements or sensory activation. They may not alter the respiratory pattern and therefore may be considered as spontaneous. However many emotional responses alter the respiratory patterns such as laughter, crying or shouting.

Given the presence of the response to such multiple and diverse stimuli it is tempting to abandon the use of the sympathetic response for any clinical purpose or even to give up a physiological interpretation. What can those seemingly different stimuli have in common? The obvious answer to us is that they all activate the sympathetic nervous system. They all induce a general autonomic sympathetic arousal.[3] The generation of the SSR by a self-generated movement, by a sensory signal or by a mental or emotional stress should be seen as a part of a generalized sympathetic response that may include tachycardia, vasomotor activation with an increase in blood pressure and activation of the sudomotor glands.

In addition, it does not seem too unlikely that the activation of the sudomotor glands of the glabrous skin may also have a thermoregulatory function. Their response to several kinds of thermal stimuli should be studied in the future. We found that the cold face test is a powerful activator of the SSR. The activation of the sudomotor glands of non-hairy skin during emotional and cognitive actions does not seem to be a useless sympathetic epiphenomenon but part of a generalized orienting response. The activation of the sudomotor glands is useful to the body as a mechanism for dissipating heat during the activities related to emotions and movements, such as fleeing, fighting or others.

Our study also sheds some light in the confounding factors in the generation and clinical application of the SSR. The response is exquisitely sensitive to respiratory changes and therefore the respiratory movements should always be included in the records. It should not be considered spontaneous unless a respiratory change is not clearly seen. The response should be preferably obtained with the eyes closed. When the subject opens the eyes and explores the surroundings the response readily appears. The SSR should be obtained ideally in a noise-isolated chamber given the fact that it is easily produced by any unexpected noise. Verbal instructions generate the response. After an instruction is given the trace should be observed for the response and the demanded maneuver should be performed 10 or more seconds later. Somnolence is perhaps the most common cause that the response is not obtained even if the stimulus is given one minute apart. Some studies in the future should address this problem with simultaneous EEG recordings. A quantifiable stimulus must be used in order to measure the latency of the reflex such as eye opening, muscle contraction, acoustic stimulus, cough or an electrical or magnetic pulse. The study of the response may be more useful when studied in conjunction with the heart rate, skin blood flow, blood pressure and other physiological variables. If used in conjunction with other physiological variables it may prove highly useful in psychophysiological studies. The isolated study of the SSR is useful for the determination of the integrity of the sympathetic skin outflow to the sudomotor glands and as a general method of assessment of the sympathetic C efferent fibers.

Our proposed classification of the stimuli that induce the SSR in non-physiological, physiological (induced by internal and external signals, movement-related and sensory-related) and emotional or cognitive may be of some heuristic value in the study of this most complex response.

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