Unraveling the sensitive brain

a review on Sensory Processing Sensitivity and its underlying mechanisms

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Summary

Sensory Processing Sensitivity (SPS) is an innate character temperament that has been described as an environmental sensitivity theory and is characterized by the abbreviation DOES: Depth of processing, ease of Overstimulation, Emotional reactivity and Sensitivity to stimuli. Despite the fact that neurobiological research on SPS is still in its infancy, results are supporting that Highly Sensitive Persons (HSPs) show higher levels of alertness and awareness, attention to detail and emotional reactivity. Results on depth of processing are more tentative, but evidence of brain activation in areas involved in higher order cognitive processing has been found in association with high SPS scores.

The functioning of an HSP is strongly influenced by their environment. A positive environment (such as high quality of parenting) can benefit an HSP by enhancing their higher order cognitive processing, reflective thinking, calm and awareness, while a negative environment can diminish these aspects and increase the chances of an HSP developing anxiety or depression. Since SPS has behavioral comparisons to anxiety and depression, research on the cause of SPS is often sought in the same mechanisms that are known for anxiety. Despite there not being much results yet, suggestions have been made on the involvement of a more sensitive central nervous system, the serotonin transporter gene 5-HTTLPR, levels of the GABA neurotransmitter and the HPA-axis on the underlying mechanisms of SPS.

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Introduction

Day to day occupations such as going to school or work, planning and maintaining social relationships are inherently part of living. For many people these things are fairly standard occupations, but for other people they are more complex and intense experiences. These people are highly sensitive to stimuli, which makes them notice more details and process them deeper. This can result in overhearing the conversations of the people next to them on the bus, thinking longer and harder in a meeting where many colleagues have an opinion and, when being in a restaurant for example, not only paying attention to the food, but also to the lighting, music, an uncomfortable chair and the mood of their waiter. Besides noticing these stimuli more, sensitive people are also more affected by them.

People that are more than average aware of subtle stimuli are Highly Sensitive Persons (HSPs), or: people with the Sensory Processing Sensitivity (SPS) trait. SPS is an innate temperament trait, first described in 1997, that is found in approximately 20% of the human population (Aron & Aron, 1997). The SPS trait is characterized by four core aspects: depth of processing, ease of overstimulation, emotional reactivity and sensitivity to stimuli (Aron et al., 2012; Aron & Aron, 1997). HSPs notice more (subtle) details in their environment, such as sounds, smells and visual stimuli, compared to non-HSPs. They also have a strong feeling of interoception, a strong intuition and are fairly good at sensing the ambiance and other people's moods in social contexts (Aron et al., 2012; Ujiie & Takahashi, 2022).

Because of this noticing of more stimuli while simultaneously processing them deeper and also having stronger emotional reactions, HSPs need more time for processing, thinking, and recovering from stimuli and emotions compared to non-HSPs (Aron et al., 2012). This can be manifested by taking time to rest and reflect. When their needs for rest and reflection are not being met, HSPs can be overstimulated by for example certain tastes, bright lights, sounds or changes. Besides these fairly objective stimuli, HSPs tend to be influenced by other people's moods. When people in their environment are in a certain mood, HSPs are affected by these feelings and tend to alter their own mood accordingly (Acevedo et al., 2014).

HSPs are thus strongly affected by stimuli from their environment. Research has shown that these effects are not only stronger in negative environments or situations, but also for positive experiences or interventions (Boyce & Ellis, 2005; Greven et al., 2019; Pluess, 2015). This makes it very interesting to investigate more about the functional brain activity area in SPS, not only to prevent HSPs from being affected negatively, but also for optimizing environments and interventions that could be used for HSPs as well as for non-HSPs.

This thesis aims to investigate the trait of SPS and its underlying neurocircuitry. Theory and background on SPS will be discussed, as well as neuroimaging results on SPS. Lastly, relevant genetics and neurochemistry will be discussed.

The ‘DOES’ aspects of Sensory Processing Sensitivity

Sensory Processing Sensitivity (SPS) is a character temperament that was first described by Elaine Aron (1997), when she conducted questionnaires from people that described themselves as being more sensitive than others in their environment. More sensitive people felt easily overstimulated by loud noises, bright lights or stressful periods, had a complex inner life and were very conscientious, tended to react more carefully to new or unexpected circumstances and experienced high emotional reactivity. This led Aron to distinguish SPS as a temperament that is characterized by greater awareness of environmental subtleties, greater depth of processing, ease of overstimulation and increased emotional reactivity and empathy, which is now thought to be driven by a more sensitive central nervous system (Aron et al., 1997; 2012; Homberg et al., 2016). Aron described these four core traits of SPS by the abbreviation DOES (Aron et al., 2010; 2012): Deeper processing, Ease of Overstimulation, Empathy/Emotional reactivity and Sensitivity to stimuli. The trait of sensitivity is found in roughly 20% of the human population (Aron et al., 2012).

Sensitivity to stimuli is not about sensitivity of the sensory organs, but is about the ability to filter relevant information, so it is rather about the processing of stimuli and increased activity in attentional processes in the brain. Because of this increased attention, Highly Sensitive Persons (HSPs) generally tend to perceive more details and information from their environment than non-HSPs (Aron et al., 2010). Especially in new environments, but also when faced with choices or unexpected stimuli, HSPs tend to pause before they act, which Aron describes as ‘pausing to check’, caused by a moment to compare expected stimuli to actual stimuli (Aron et al., 2010; Gray & McNaughton, 2000; Jagiellowicz et al., 2011). HSPs are not only sensitive to external stimuli, but also to internal stimuli such as hunger and pain (Acevedo et al., 2017; Aron et al., 2010).

The aspect of depth of processing in SPS has not been elaborately researched on a (neuro)biological level yet, but behavioral research and functional MRI studies have found some tentative evidence on the depth of processing , which will be discussed later. However, Aron states that depth of processing is stronger for HSPs (Aron et al., 2012; Aron & Aron, 1997). HSPs tend to think more thoroughly on choices and problems, but also seem to process sensory stimuli on a deeper level, which results in HSP generally having a more rich and complex inner life compared to non HSPs (Aron et al., 2012). Despite not being neurologically investigated thoroughly, the aspects of deeper processing seem to be found in behavioral research and questionnaires and are therefore also included in the HSP scale, a questionnaire to assess SPS, which will be discussed later (Aron et al., 1997; 2012).

In addition, SPS is characterized by Empathy or Emotional reactivity. HSPs generally experience more and stronger emotions to the stimuli they perceive compared to non-HSPs. They are easily affected by other people’s moods or the ambiance in social situations, which makes them generally more empathetic and compassionate compared to non-HSPs (Aron et al., 1997; 2012). As shown in **figure 1**, depth of processing and emotional reactivity seem to enhance each other greatly in SPS, which is in agreement with research that has shown that emotional reactivity facilitates learning and memory by providing feedback and retrospective appraisal, which is in turn associated with depth of processing (Aron et al., 2012; Baumeister et al., 2007).

When heightened sensitivity, strong emotions and deeper processing come together, an HSP might feel overstimulated more easily. This can occur from certain stimuli that easily cross the HSPs low sensory threshold as well as from too many different stimuli that all are being processed simultaneously or the strong emotions they experience. As a result of overstimulation, HSPs can experience high levels of stress and cognitive depletion (Acevedo et al., 2021; Aron et al., 2012), causing them to function less optimally. To overcome overstimulation, HSPs need rest and downtime in order to be able to keep functioning in their daily life.

Perspectives on individual differences

Looking at individual differences on the aspect of Sensory Processing Sensitivity is a perspective that is different from previous perspectives on individual differences. A few well known perspectives are coping strategies and the big five personalities, which both have aspects that seem to be comparable to aspects of SPS. However, they are not the same, but might help understanding the perspective of SPS on individual differences.

Coping strategies

In animals, coping strategies have been elaborately researched (Aron et al., 2012; Koolhaas et al., 1999; Schjolden & Winberg, 2007; Suomi, 1997; Wilson et al., 1993). Two main strategies can be found: the proactive and the reactive strategy. A proactive animal will act fast if needed, without taking too much details of the environment into account. These animals are often seen as more bold, because they respond quickly to (sudden) cues from the environment and take larger risks. A reactive animal however, takes more time to assess cues from the environment before acting. These animals generally seem less bold and more shy and show inhibition of behavior, especially in new situations or conflict. Despite seeming more shy, after taking time to observe these animals often show a more bold behavior in the future that might appear more risky, but is actually caused by more certainty because these animals compare outcomes of past and future events (Koolhaas et al., 1999).

The characteristics of reactive animals are found to be useful when trying to find optimal habitats, food resources, looking out for predators and engaging in social behavior (Greven et al., 2019). However there too are downsides to for example observing rather than acting quickly, since this generally lacks assertive and exploring behavior, which is essential for a population. Therefore a balance is needed between proactive and reactive animals in a population, making both a frequency dependent trait.

Coping styles are relevant to the SPS theory because, according to Aron et al. (2012), the 'pausing to check' aspect, or inhibition of behavior, of SPS is comparable to the reactive coping style. The behavior of observing and comparing past, present and future situations seems to be enhanced in SPS and results in comparable beneficial outcomes for a population or group, such as engagement in social behavior and well-considered decision making (Aron et al., 2012).

The aspect of 'inhibition of behavior' (in humans) has its foundation in *Gray's reinforcement sensitivity theory* (Gray, 1982), in which the Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS) are described. Gray proposed that the BIS mediated reactivity to conditioned punishment and non-reward while the BAS reacted to conditioned stimuli on reward of relief from punishment and underlies positive emotions. However in 2000 the theory was revised and where BAS remained the same, BIS was now thought to be responsible for the inhibition of ongoing behavior in the service of conflict detection and resolution (Gray & McNaughton, 2000). Thus, the BIS is to compare actual with expected stimuli, which results in a temporary inhibition of activity. When there is a mismatch, unexpected or averse stimuli, there will be a complete stop or 'freeze' rather than a pause in (exploring) behavior (Aron & Aron, 1997). Especially BIS is related to the reactive coping style and also SPS, given the inhibition or 'pausing to check' aspect in behavior. Smolewska et al. (2006) showed that BIS activity indeed is positively associated with SPS.

The big five personalities

Another way of looking at individual differences is by using personality constructs such as 'The Big Five', which is well known and supported within psychology (Costa & McCrae, 1992). It consists of five continuums on different personality aspects, which are used to describe and understand an individual's characteristics, behavior and perhaps challenges in functioning: openness to experience (inventive/curious vs. consistent/cautious), conscientiousness (efficient/organized vs. extravagant/careless), extraversion (outgoing/energetic vs. solitary/reserved), agreeableness (friendly/compassionate vs. critical/rational) and neuroticism (sensitive/nervous vs.

resilient/confident). An individual can, on each continuum, score more to one side rather than the other, which gives accurate information on their personality, strengths and weaknesses.

There has been, and still is, an ongoing discussion about the origin of an individual's personality; whether it is mostly formed by genes or by environment. Research has shown that at least a part is determined by genes, but the influence of the environment also has a strong effect on the development of certain personality traits (Jang et al., 1996).

The Big Five are relevant to the theory of SPS, since aspects of The Five such as introversion and neuroticism are often being compared to traits of HSPs (Aron et al., 2012; Aron & Aron, 1997). Smolewska et al. (2006) performed research on the relation between SPS and The Big Five, in which they found that SPS was significantly associated with Neuroticism and had some association with Openness to Experience, but no significant relation to one's level of Extraversion, Agreeableness or Conscientiousness. As will be discussed more elaborately later, maldevelopment of SPS is associated with mood disorders such as depression, which is also found in individuals scoring higher on neuroticism for example. This explains why research on SPS often control their results for high scores on neuroticism and depression.

According to Aron, before their first description of SPS (1997), it had been confused or subsumed in previous theorizing by personality researchers. In a series of 7 studies, Aron & Aron (1997) have demonstrated however that SPS is partially independent from introversion and emotionality. They found that sensitivity is related but not identical with social introversion, emotionality or the combination of the two. The association with these personality traits result mostly from the more visible symptoms such as ease of overstimulation, higher emotional reactivity and, as mentioned previously, pausing to check before acting. These symptoms do have overlap and as suggested by Aron, are not completely independent and share underlying environmental sensitivity theories, which will be discussed next.

The theory of Sensory Processing Sensitivity

Despite similarities and associations between SPS, coping strategies and personality constructs, the theory of SPS has a different perspective on individual differences. As previously described, its foundation lies in an individual's degree of sensitivity to their environment, as well as the processing of stimuli, both external and internal. Hence, Aron & Aron (1997) have introduced SPS as a temperament trait that is related to, but different from other temperament and personality constructs. The theory of SPS is related to environmental sensitivity theories of which several explain underlying mechanisms that are also found in SPS. As said, these environmental theories are also related to other personality constructs, which explains the associations that are often found. However, here they will be discussed in the light of SPS.

The first model, the *Diathesis-Stress Model* (Belsky & Pluess, 2009; Ellis et al., 2011) poses that certain individuals are more prone to suffer consequences from negative environments or experiences because of their individual risk factors, such as genes. This model resembles thoughts about SPS that were mainly focused on the more visible aspects of SPS, which were perceived as negative consequences of sensitivity to the environment. However, HSPs do not only react more strongly to a negative environment, but also to positive environments and experiences, such as interventions (Lionetti et al., 2018; Pluess & Boniwell, 2015a). This second aspect resembles the *Vantage Sensitivity* theory (de Villiers et al., 2018; Pluess, 2017), which states that higher sensitivity to the environment results in a larger benefit from a positive environment. Since for SPS both theories seem relevant, the theory of *Differential Susceptibility* (Belsky, 1997; Belsky & Pluess, 2009) captures the essence of SPS best. This theory combines the two previous theories and states that higher sensitivity to the environment can result in a stronger response and thus suffering or benefit from either negative or positive environments. This theory of Differential Susceptibility focuses mainly on the phenotypical temperament and the genetics underlying the sensitivity and response on the environment.

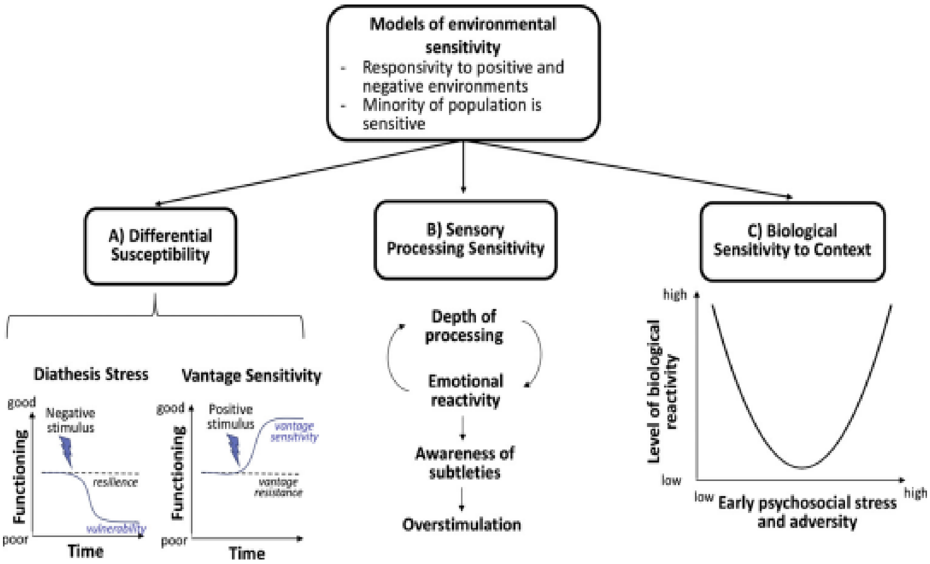


Figure 1. Models of environmental sensitivity that all describe individual differences in sensitivity to both positive and negative environments. All hypothesize a minority of the population to express higher sensitivity.
A) *Differential Susceptibility*: combines *Diathesis stress* and *Vantage Sensitivity* which focus on response to adverse and positive environments respectively.
B) *Sensory Processing Sensitivity*: temperament trait that combines depth of processing, ease of overstimulation, emotional reactivity and sensitivity to stimuli.
C) *Biological Sensitivity to context*: Sensitivity as a biological property with emphasis on heightened reactivity in the stress response system. Focuses on early development environments.
(Greven et al., 2019)

In contrast, the theory of *Biological Sensitivity to Context* (Boyce & Ellis, 2005) focuses strongly on the physical aspect of sensitivity and response. This theory poses that a more sensitive stress response system can make an individual more susceptible to negative environments. However, it too poses that these stress response systems can also have beneficial effects. This theory focuses more on early development and the environmental influences during infancy, and is in line with the findings of Homberg et al. (2016), who have shown that individuals with SPS have a more sensitive central nervous system.

Development of SPS

Research has found that experiences during infancy are indeed having a strong influence later on in the life of individuals with SPS (Acevedo et al., 2017). HSP adults experience stronger negative effects as a result of low quality childhood, and dealing with adverse circumstances during childhood might result in atypical development, in which the HSPs develop a higher risk for behavioral problems and psychopathologies such as depression, anxiety and neuroticism in both childhood and adulthood (Acevedo et al., 2017; Booth et al., 2015; Liss et al., 2005). Such a development can have a strong negative influence on an individual's well-being, hindering their daily functioning. However, research by Acevedo et al. (2017) has also shown that HSPs benefit from high quality childhood by having a higher reward response and developing adaptive responsivity to emotionally evocative stimuli, meaning they are more capable at self-controlling and staying calm. Results of Acevedo et al. will be discussed more elaborately later. Furthermore, interventions such as therapy or meditation have strong positive effects on HSPs (Nocentini et al., 2018; Pluess & Boniwell, 2015b), which shows that negative aspects of the trait can be managed or treated to benefit an HSPs functioning.

Thus even though HSPs have unique beneficial characteristics that can help not only themselves but also their social environment thrive, good management of characteristics and (cognitive) energy is needed to prevent experiencing the downsides of the SPS trait.

Assessment of Sensory Processing Sensitivity

SPS can be assessed in adults by taking a test called the HSP scale, which was generated by Aron & Aron (1997) when conducting their first published research on SPS. This test consists of 27 questions which can be answered with either yes or no (for full questionnaire, see appendix). When answered 'yes' 14 times or more, a person is considered highly sensitive. The HSP scale is found to be significant to assess whether a person is highly sensitive and is used in many research on the SPS trait (Aron et al., 2010; Aron & Aron, 1997). However, in research a shorter version of the HSP scale is often used. This test generally contains only 11 of the 27 questions, since the scale with 11 questions has high correlations with the overall scale total (Aron et al., 2010). The HSP scale first was thought to be unidimensional, but researchers have proposed that it consists of three subscales: low sensory threshold (LST, i.e. sensitivity to subtle external stimuli), Ease of Excitation (EOE, i.e. being easily overwhelmed by internal and external stimuli) and Aestathic Sensitivity (AES, i.e. openness for, and pleasure of, aesthetic experiences and positive stimuli) (Greven et al., 2019; Lionetti et al., 2018; Pluess et al., 2018). The HSP scale is still being used to assess SPS, although research often mention the three subscales and the associations to their results separately when discussing certain aspects of the trait. In 2021, Malinakova et al. have proposed a new questionnaire: the Sensory Processing Sensitivity Questionnaire. They found that the questionnaire has good psychometric characteristics, namely 'high temporal stability and excellent internal consistency'.

In addition to the HSP scale, there also is a scale for sensitive children: the Highly Sensitive Child (HSC) scale (Pluess et al., 2018) .This test contains 11 questions which can be answered by the child with either yes or no, similarly to the HSP scale. Furthermore there is a questionnaire which parents can take if their child is not old enough to take the test or as a second opinion on the HSC test (Aron, 2002).

Functional imaging research on SPS

Research on SPS has been mostly descriptive and psychological for a long period, which has led to an accepted description of the trait, including its benefits and costs. More recently, biological and neurological research are being performed to investigate the underlying biology of the trait. Despite this research still being in its infancy, it has already shown results that seem to support the 'DOES' aspects of SPS. Greven et al. (2019) have reviewed theory and research on SPS and suggest that the characteristic features of increased emotionality and empathy (e.g. insula, claustrum, amygdala, cingulate cortex) and the deep information processing (e.g. precuneus, prefrontal cortex, inferior frontal gyrus (IFG)) are interestingly corresponding to the salience network and default mode network, respectively, which mediate attention to salient and emotional stimuli as well as internal mentation – 'the introspective and adaptive mental activities in which humans spontaneously and deliberately engage in everyday' (Andrews-Hanna, 2012) (**fig. 2**). Enhanced awareness and attention to stimuli in SPS have been supported most by brain imaging results, as well as strong emotional reactivity. Evidence of enhanced depth of processing in SPS is still preliminary and needs more investigation. However, suggestions have been made, which will be discussed here after the results on awareness, attention and emotional reactivity.

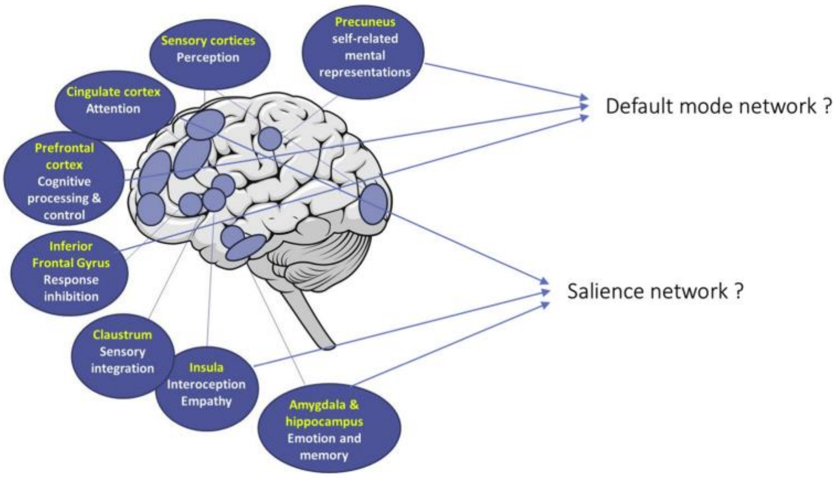


Figure 2. The activity patterns in the brain of HSPs point towards increased emotionality and empathy (e.g. insula, claustrum, amygdala, cingulate cortex) and deep information processing (e.g. precuneus, prefrontal cortex, inferior frontal gyrus), which are the core facets of SPS. Interestingly, these clusters of brain regions correspond to the salience and default mode networks respectively.
(Greven et al., 2019)

Attention and awareness

Most of the neurological research show results that support the association between SPS and enhanced awareness and attention (Acevedo et al., 2014, 2017, 2021; A. Aron et al., 2010; Jagiellowicz et al., 2011). In 2010, Aron et al. used results from Hedden et al. (2008) on a research that investigated the influence of culture on the performance on absolute VS relative tasks. In this research, Americans and East Asians performed tasks in which they had to make both relative and absolute judgements. Relative tasks, where context has to be taken into account, is generally preferred by Asian culture, whereas absolute tasks, where context has to be ignored, is generally preferred by American culture. Results showed that for relevant regions of interest, Asians showed enhanced brain activation for their non-preferred task compared to their preferred task. Americans showed the same results: more activation at their non-preferred task and less at their preferred task. The results indicated that culture had an effect on the processing and performance of a task. However, when Aron in 2010 controlled these results for SPS, culture did not cause a difference in performance, as seen in **figure 3**. Subjects scoring higher on SPS hardly showed differences in brain activation, regardless the task they were performing. Brain activation was at a same level at preferred and non-preferred tasks for HSPs. These results indicate that HSPs generally pay the same level of attention to stimuli, at some points relatively more than non-HSPs, regardless their preference of task or cultural influence.

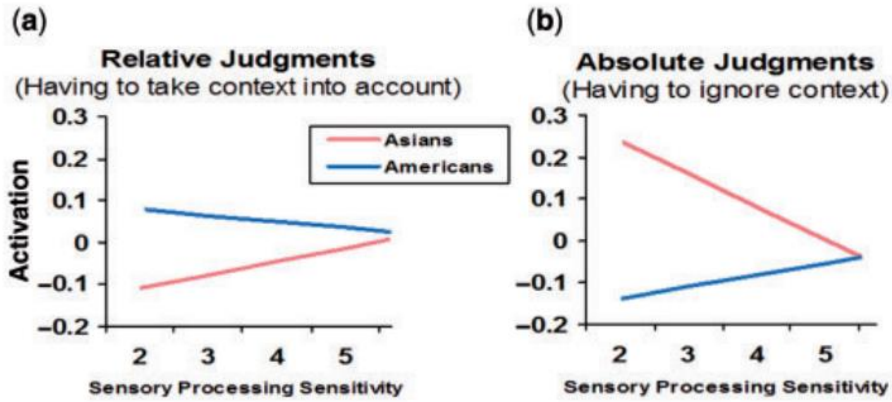


Figure 3. Regression lines for each cultural group showing neural activity as a function of SPS scores. (a) Relative task. (b) Absolute task. (Aron et al., 2010)

Other research by Jagiellowicz et al. (2011) investigated SPS and visual processing. Subjects had to detect small and large changes in pictures of scenes while brain activation and reaction time (RT) were measured. Results showed that as a function of SPS, RT were longer for minor changes vs. major changes. The longer RT at smaller changes is in line with theory suggesting that HSPs look more elaborately at details in a scene. Results also showed enhanced brain activation in regions that are relevant for detecting subtle change. Activation associated with SPS was found in areas associated with visual processing (claustrum), object recognition (occipital and temporal lobes, precuneus), oculomotor guidance (right cerebellum) and shift of attention (intraparietal sulcus (IPS), temporoparietal junction (TPJ), precentral sulcus). Thus strong and significant association with individual differences in SPS were found in the temporal lobe, claustrum and cerebellum. The significant activation in these areas support theory that HSPs spend more attention and time on detecting subtle stimuli than non-HSPs. **Figure 4** shows this research's significant activation differences associated with SPS.

Gerstenberg (2012) too investigated the relation between SPS and higher order visual processing by asking subjects to seek and tell whether a target was or was not present in a scene. Contrary to Jagiellowicz et al., Gerstenberg found that SPS was related to shorter reaction times, for both target present and not present conditions. He explains this difference by the fact that perhaps their tasks were less complicated than those of Jagiellowicz et al. He suggests that HSPs take more time to respond to complex differences while they are quicker to detect simple differences, which is still in line with Jagiellowicz's results.

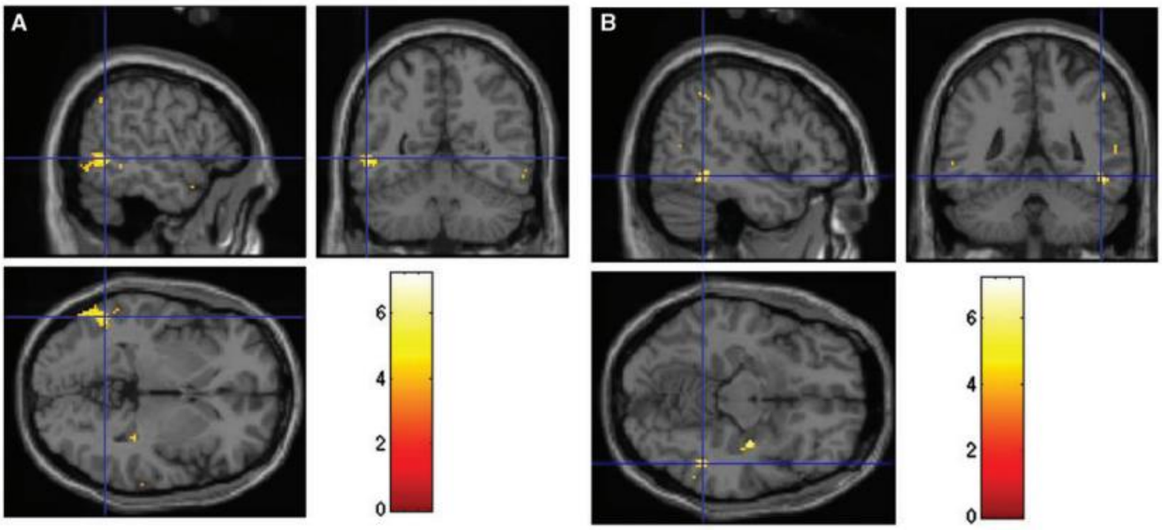


Fig 4. Activation for the association of SPS with the minor change less than major change condition in the (A) left middle temporal lobe and the (B) right subgyral temporal lobe. Lighter color corresponds to greater activation. (Jagiellowicz et al., 2011)

Acevedo et al. (2014) investigated emotional reactivity and its connection with SPS by showing subjects images of their partners and strangers showing happy, neutral and sad facial expressions. She investigated whether different images evoked different brain activation, since theory on SPS suggests that social stimuli are important to HSPs and should thus evoke stronger brain activation. Acevedo did find associations between SPS and activation regarding social stimuli, which will be discussed more elaborately later, but she also found brain activation regarding attention and awareness that was associated with SPS. They found SPS associated activation for all conditions (partner vs. stranger, happy vs. sad) in areas involved in attention and action planning (cingulate and premotor area (PMA)), and on attention and alertness (cingulate and insulate). Pausing to check seemed to be reflected by activation in the PMA and prefrontal cortex (PFC). She also found stronger activation in the middle temporal gyrus (MTG), which is associated with awareness to stimuli and is described as a semantic hub for language, auditory and visual processing (Binder et al., 2009; Dronkers et al., 2004). These results too support theory of SPS being associated with greater awareness and responsiveness since activation was found in areas that are involved in sensory information processing and integration, action planning and overall awareness.

In 2022, Hoffmann et al. performed a research in which they investigated the influence of high SPS scores on inhibitory control. They had subjects perform antisaccade paradigms, because this exercise can be used to measure inhibition of the frontal lobe on reflex behavior, and thus can be used to measure the level of inhibitory control. One of the paradigms had images of small geometrical shapes, while the other consisted of images of faces showing emotions. Regarding attention and awareness, Hoffmann et al. found that SPS predicted a faster processing speed and higher accuracy on the emotional face antisaccade task, while for the small geometrical shape saccade task SPS did not predict shorter RT. This result, which is in line with the findings of Jagiellowicz et al. (2011), suggests that indeed HSPs take more time to observe smaller details in comparison to larger images.

Emotional reactivity

Shorter RT associated with SPS during the emotional face antisaccade task in Hoffmann's (2022) research shows a faster processing of (bigger) facial stimuli in comparison to smaller geometric shapes. This result might support the importance of emotional stimuli and social behavior to HSPs, which is often mentioned in self-reports and has been accepted as a certain feature of SPS (Aron et al., 2012; Greven et al., 2019)

SPS associated reaction to emotional stimuli has been investigated more elaborately by Acevedo et al. (2014, 2017). In their 2014 research on the processing of positive and negative emotional stimuli from partners and strangers, they found that during the presentation of close others (vs. strangers) and positive images (vs. neutral or sad) HSP scores were associated with a stronger activation of brain areas involved in self-other processing, awareness and empathy (e.g., insula, inferior frontal gyrus (IFG), cingulate, middle temporal gyrus (MTG), dorsolateral prefrontal cortex (DLFPC) and the premotor area (PMA)). The connection between the insula and the IFG is interesting since the IFG is involved in emotion detection and interpretation, and is suggested to be part of the Mirror Neuron System (MNS), which is relevant to SPS since it is a group of neurons that 'mirrors' the behavior and actions of others. (Iacoboni et al., 1999; Jabbi & Keysers, 2008; van Overwalle & Baetens, 2009). The MNS is involved in neurocognitive functions such as empathy, theory of mind and social cognition, which are features comparable to those of SPS (Rajmohan & Mohandas, 2007). The activations in this research suggest associations between SPS and intuitively sensing other's goals and intentions, as well as own thoughts and feelings, which results in the previously described ability to be more responsive to others moods, especially individuals close to the HSPs.

In 2017, Acevedo et al. performed new research on SPS and emotional reactivity. This time they had subjects look at both images from the IAPS (International Affective Picture System) associated with both negative and positive emotions during brain scanning and rating their anxiety after seeing an image. Not only brain activation in reaction to the images and the association with SPS were measured, but also quality of childhood parenting (QCP) was taken into account. Results showed that for emotional (vs. neutral) images, SPS and QCP were associated with significant activation in the hypothalamus, temporal and parietal areas, the hippocampus and the entorhinal cortex (EC). These regions are involved in physiological homeostasis, integration of information, awareness and reflective thinking, as well as the processing of emotional memory and learning. In association with positive emotional images, SPS was significantly correlated with areas involved in self-other integration (insula and IFG), reward processing (ventral tegmental area (VTA), substantia nigra (SN), caudate), satiation (subcallosal AC) and calm (periaqueductal gray (PAG)) (**fig. 5**). Activation was found to a greater extend with increasing QCP. In association with negative emotional images, SPS and QCP showed significant activation in the amygdala and prefrontal cortex, which are involved in emotion and self-control (**fig. 6**). When only controlling for SPS, reward activity is diminished upon negative stimuli (**fig. 7**). However, while taking not only SPS but also QCP into account, reward activity was not diminished. Acevedo et al state that since high SPS with high QCP induced the strongest activations in the hypothalamus, EC and hippocampus in response to both positive **(fig. 5)** and negative (**fig. 6**) stimuli, positive environments (e.g. high QCP) may indeed enhance positive effects of SPS via greater emotion, memory and physiological homeostasis. Acevedo et al. conclude that SPS (and QCP) is positively associated with activation of brain areas involved in depth of processing, memory and physiological regulation in response to emotional stimuli. They state that their results support differential susceptibility and HSP models, since high QCP (a positive environment) seems to provide benefits, such as adaptive responsivity to emotionally evocative stimuli via circuits that mediate mood via reward, higher order cognitive processing (which will be discussed more elaborately next), self-regulation, reflective thinking, self/other elaboration, calm and awareness.

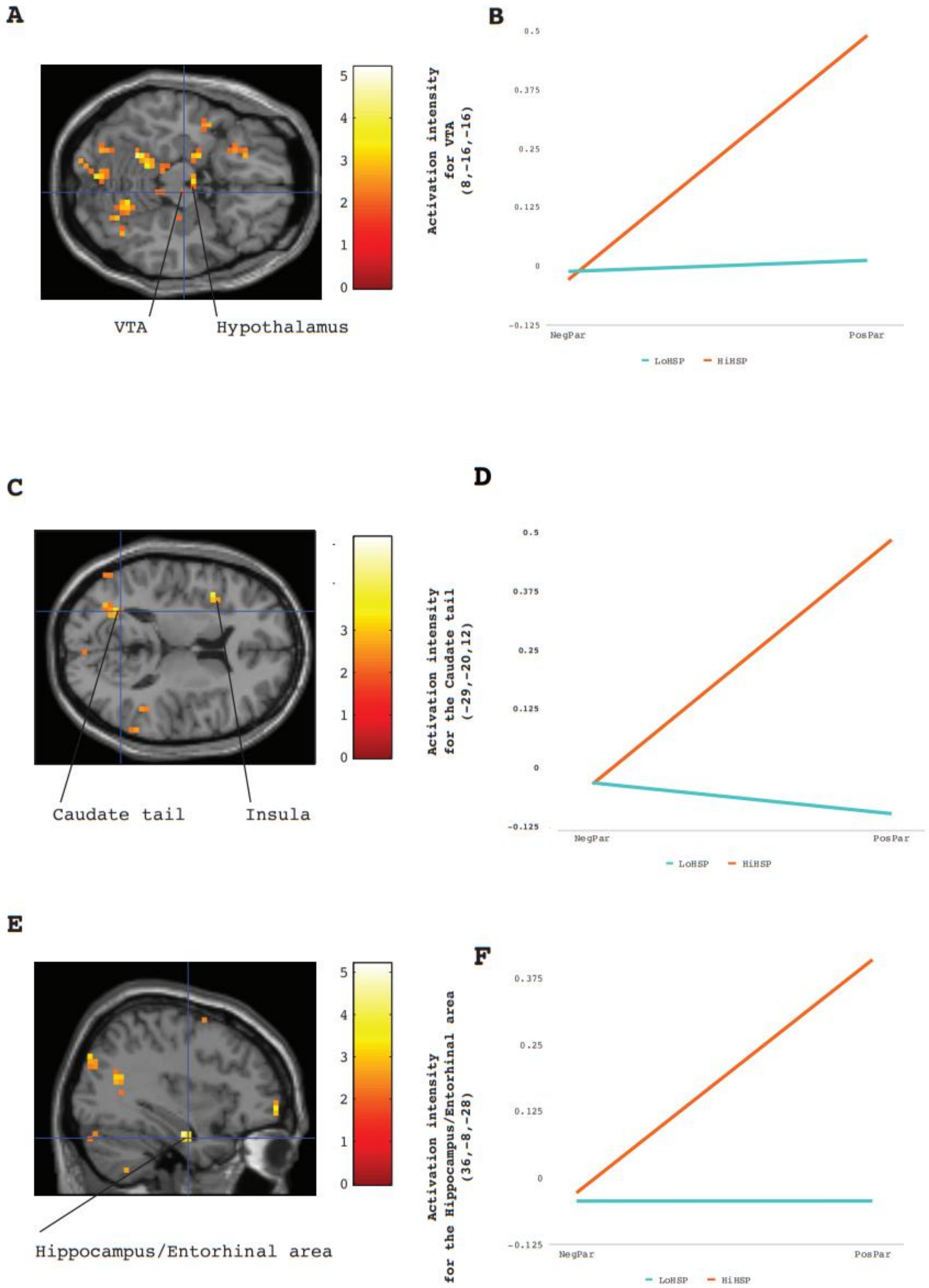


Fig 5. SPS and QCP interaction is associated with brain responsivity to positive (vs. neutral) images in the (A) ventral tegmental area (VTA)/substantia nigra (SN) and hypothalamus, (C) the caudate tail and insula, and (E) the hippocampus/entorhinal area. Plots show that positive childhood moderates the response intensity in the (B) R. VTA/SN, (D) the L. caudate tail, and (F) the R. hippocampus/entorhinal area. (Acevedo et al., 2017)

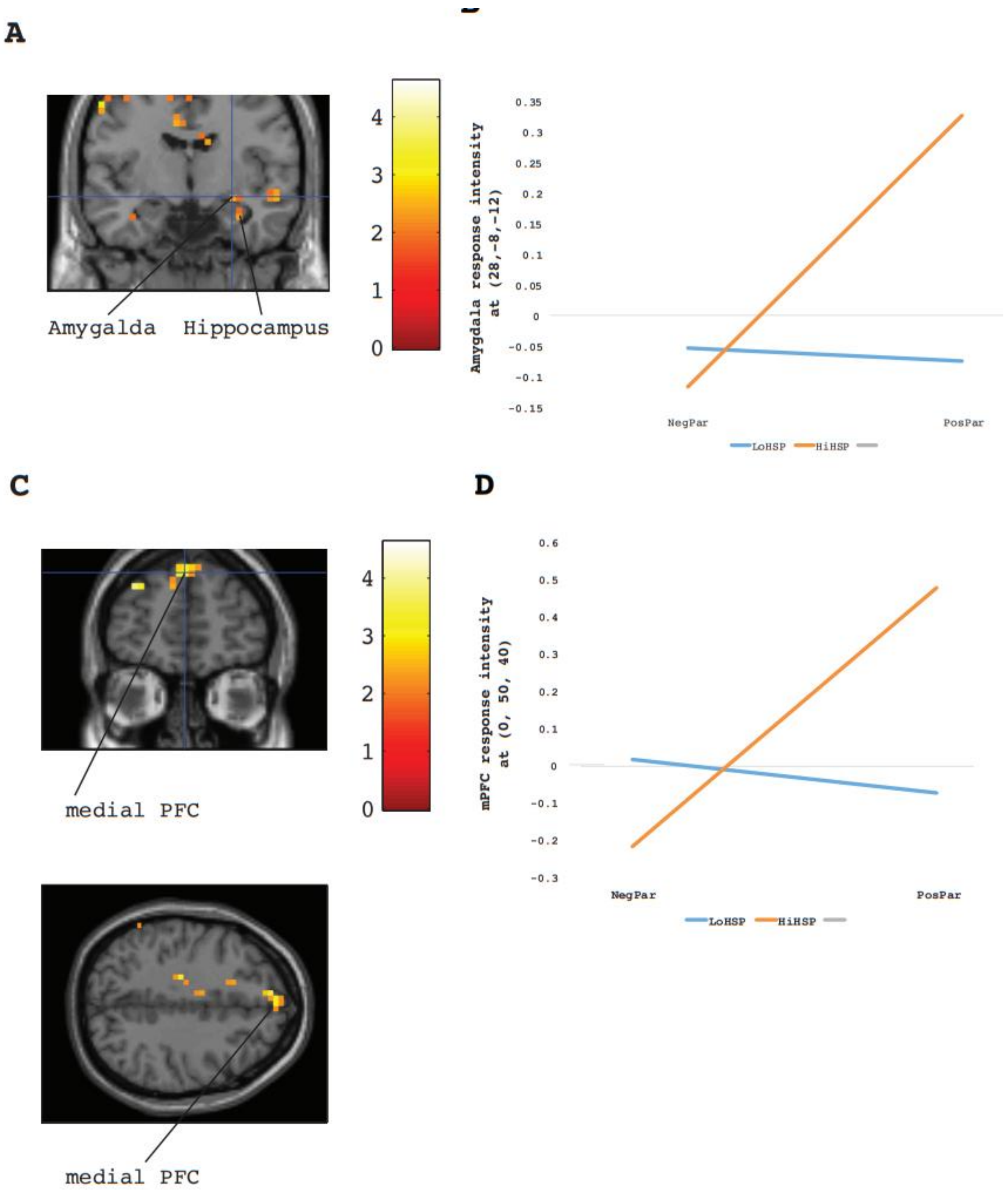


Figure 6. SPS X QCP interaction is associated with brain responsivity to negative (vs. neutral) images in the (A) amygdala and hippocampus and (C) the medial PFC. Plots show that positive childhood moderates the response intensity in the (B) R. amygdala and (D) the L. medial PFC. (Acevedo et al., 2017)

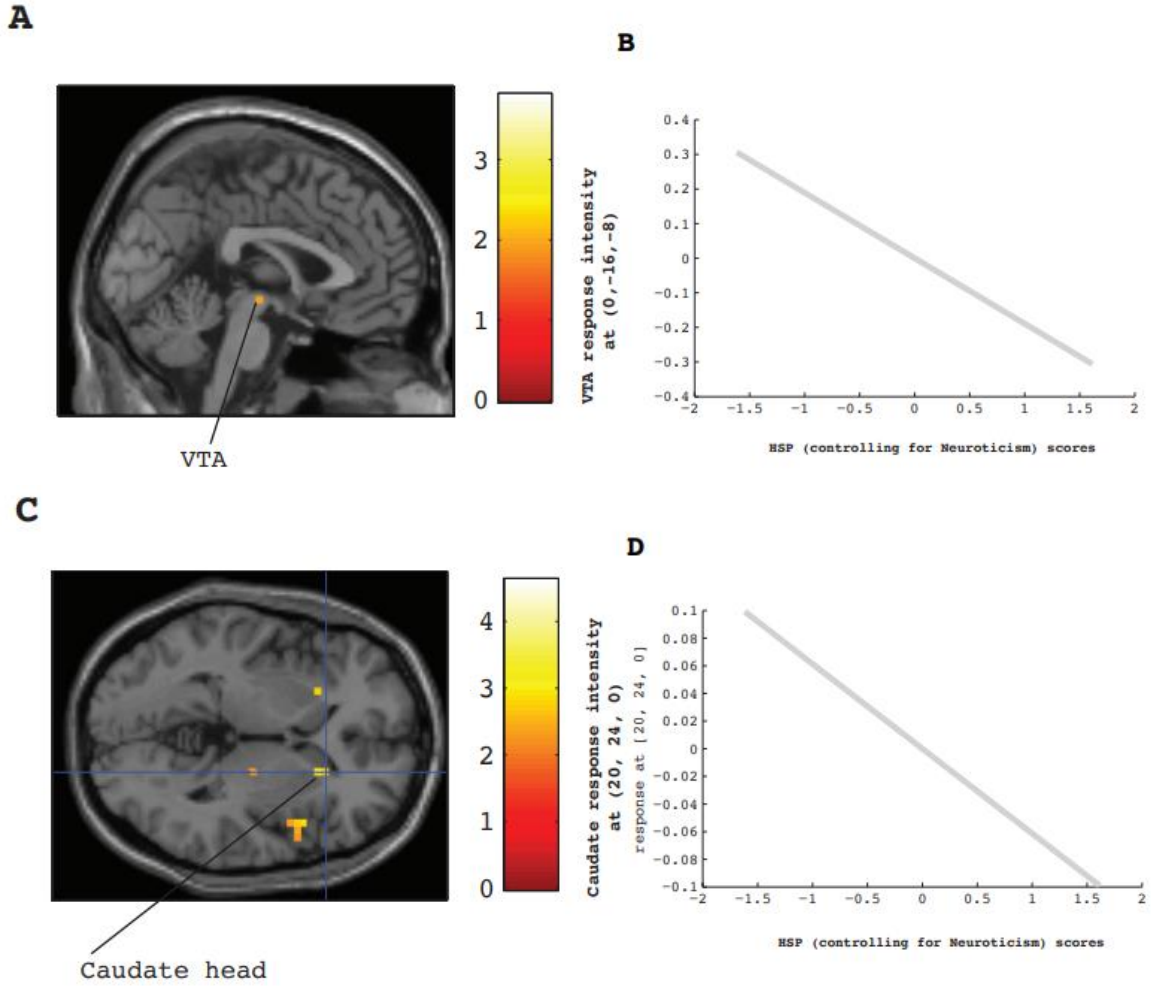


Figure 7. SPS is associated with decreased reward response to negative (vs. neutral) images in the (A) VTA and (C) caudate head. Plots show decreased reward response with greater SPS in the (B) the R. VTA and (D) the R. caudate head. (Acevedo et al., 2017)

Depth of processing

As described, Acevedo et al. (2017) found evidence of high quality parenting having a positive influence on self-regulation, reflective thinking, self/other elaboration and higher order cognitive processing in association with SPS. These processes are connected to the theory of depth of processing in SPS. Acevedo et al. found that areas of the default mode network (DMN) (precuneus, parietal, temporoparietal junction (TPJ), temporal regions) were activated in association with SPS. These areas are involved in self/other elaboration, semantic representations and present-moment awareness (Schilbach et al., 2012; Spreng et al., 2009; Utevsky et al., 2014). Activation of the TPJ is of interest since it is essential for the integration of information from both the internal and external environment, is involved in interpreting others intentions and in detecting of and reorienting on environmental stimuli (Decety & Lamm, 2007; Krall et al., 2015; Saxe & Powell, 2006; van Overwalle & Baetens, 2009). Large activation clusters were seen in the temporal areas, which are associated with visual perception, semantic memory and language. Also the DMN was activated during both emotional and non-emotional tasks, indicative of more structural depth of processing instead of activation only upon emotional tasks. These results support the theory of HSPs responding adaptively to emotional stimuli through systems involving awareness, reflective thinking and self-regulation, especially in response to negative stimuli. As mentioned earlier, in their 2014 research, Acevedo et al. also found strong activation of the dorsolateral prefrontal cortex (DLPFC) in most partner contrasts and thus in response to socially relevant stimuli. This result too reflects and supports the theory of SPS and its association with deeper processing of (emotional) stimuli .

Even though results of the 2014 and 2017 research might have supported the existence of depth of processing in SPS, it was not specifically researched until 2021. Acevedo et al. (2021) then investigated whether individual differences associated with SPS could be found in resting state brain activation after a social affective task. They found strong connectivity in clusters involved in enhanced cognitive features such as cognitive processing, reflective thinking, consolidation of memory and preparation for action. A few interesting connectivity activations will be highlighted.

First there was a strong connectivity between the bilateral hippocampus and the left precuneus (**fig. 8),** which is associated with episodic memory and better performance on memory tasks. It is also associated with involuntary memory retrieval caused by perceived cues, without conscious effort (Ren et al., 2018). Thus episodic memory is amplified in subjects higher in SPS during rest after a social task. This finding supports theory that greater depth of processing (in SPS) finds place through enhanced memory processing, which ultimately supports the ability to be ready to respond adequately to future situations.

Another connectivity, between the amygdala and the periaqueductal grey (PAG), was found to be significantly negatively associated with SPS (**fig. 9**). The connection of the amygdala and PAG is essential for behaviors such as harm avoidance and prosocial behaviors (Brethel-Haurwitz et al., 2017). Furthermore, it is also involved in detecting internal physiological signals that trigger defensive behavior (Schimitel et al., 2012). Therefore, the amygdala-PAG connection also modulates states such as anxiety, panic, fear and pain, as well as attachment, protective behaviors and calm (Babaev et al., 2018; Janak & Tye, 2015). This modulation of anxiety is of interest since HSPs often show heightened anxiety (Schipper et al., 2019). The functioning of the amygdala-PAG connection has been mentioned in research on 5-HTT knockout rats, which resemble features of SPS, and the influence of GABA, since 5-HTT knockout rats showed altered activity of GABAergic neurons that signal from the amygdala to the PAG (89). The relevance of both research will be elaborated in the next section.

Another significant finding was the negative connectivity between the hippocampus and the insula (**fig. 10**). This connection is involved in emotion processing, stress regulation and mood disorders (Anteraper et al., 2014; Ghaziri et al., 2018; Phillips et al., 2003). Normally this connection is involved in a habitual stress-related connectivity pattern (Schwabe & Wolf, 2013). However in association with SPS, there is a negative connectivity between the hippocampus and the insula. This in combination with an increased connectivity between the hippocampus and the precuneus (involved in higher memory consolidation), and the hippocampus and the anterior cingulate cortex (ACC) (learned safety), is indicative of deliberate higher order processing rather than the habitual stress-related reaction. In other words: individuals high in SPS tend to process information more elaborately before acting instead of primarily acting upon reflexes.

In sum, findings of this research suggest that during rest, after engaging in a social task, HSPs show enhanced patterns of brain activity and connectivity in areas that are involved in deliberative cognitive processing, memory consolidation, attentional control and physiological homeostasis. Even though further research is required, these first results are certainly in line with theory that depth of processing is one of the cardinal features of SPS.

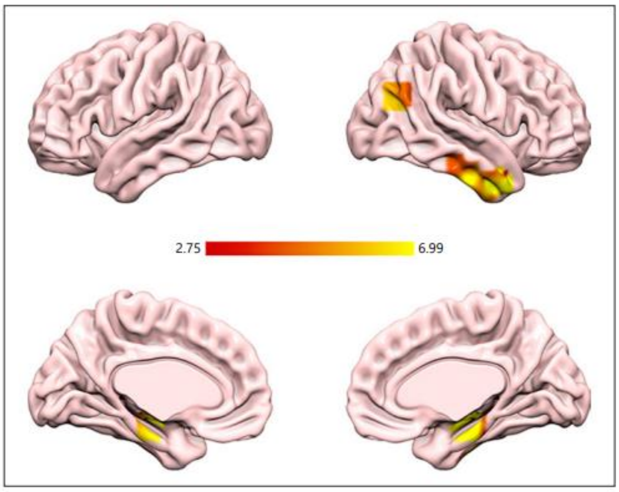


Figure 8. Increased connectivity between the left precuneus and the right hippocampus significantly correlated with higher SPS scores.
This connection is associated with episodic memory and better performance on memory tasks.
(Acevedo et al., 2021)

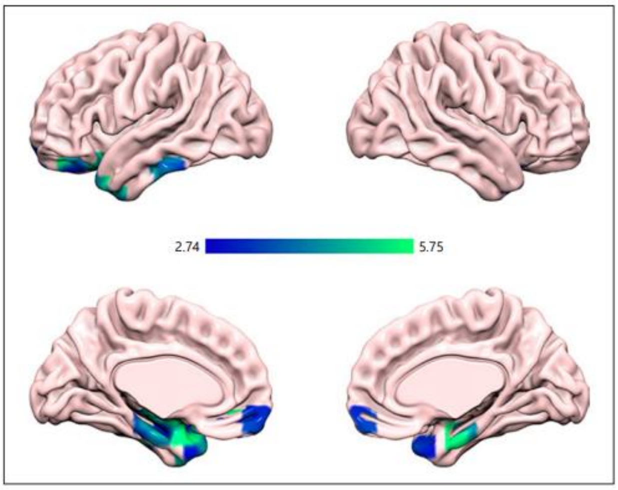


Figure 9. Negative connectivity between the right PAG and left amygdala/hippocampus significantly correlated with higher SPS scores.
The amygdala-PAG connection modulates states such as anxiety, panic, fear and pain, as well as attachment, protective behaviors and calm.
(Acevedo et al., 2021)

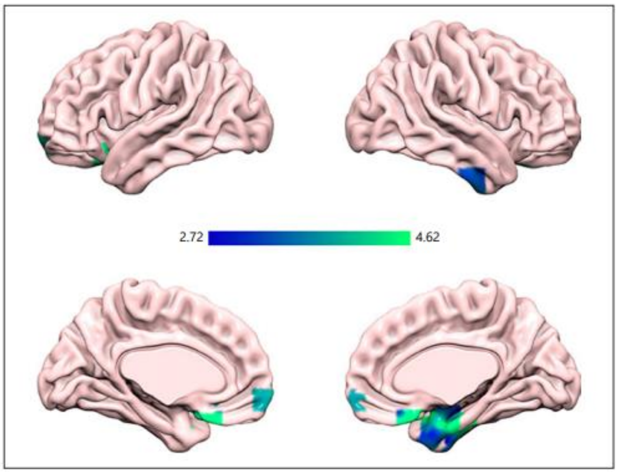


Figure 10. Negative connectivity between the right insula and right hippocampus significantly correlated with higher SPS scores.
In association with SPS, there is a negative connectivity between the hippocampus and the insula. This in combination with an increased connectivity between the hippocampus and the precuneus (fig. 9), and the hippocampus and the anterior cingulate cortex (ACC) (learned safety), is indicative of deliberate higher order processing rather than the habitual stress-related reaction.
(Acevedo et al., 2021)

Genetics and neurochemistry of SPS

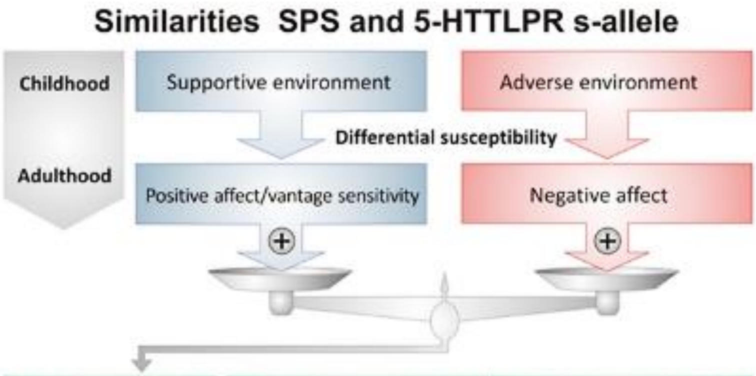
Moore & Depue (2016) have discussed the influence of several neurotransmitter (dopamine, norepinephrine, serotonin, GABA) and neuropeptide (opiates, oxytocin, corticotropin-releasing hormone) systems on environmental sensitivity. Not all of these systems have been biologically investigated in relation to SPS specifically, but the 5-HTTLPR serotonin transporter and the inhibition/excitation balance, primarily regarding GABA, as well as the HPA-axis, have been associated and discussed with regard to SPS, of which results will be highlighted next.

5-HTTLPR serotonin transporter

Since the trait of sensitivity has been evidently shown to be an evolutionary trait, the foundation of the SPS trait can be found in genes. Assary et al. (2020) have shown that SPS has a heritability of 0.47. An interesting allele associated with SPS is the serotonin transporter 5-HTTLPR allele, which mediates reuptake of serotonin after it is being released (Murphy et al., 2004). The short variant of this allele is associated with lower levels of serotonin, which results in higher emotional reactivity and susceptibility to mood disorders (Beevers et al., 2011; Homberg & Lesch, 2011; Moore & Depue, 2016; Pearson et al., 2016), of which the emotional reactivity is a clear characteristic for individuals with the SPS trait, while susceptibility to mood disorders has been correlated to HSPs with adverse childhoods (Aron et al., 2012), as previously discussed. Licht et al. (2011) found that the 5-HTTLPR short/short (s/s) genotype was associated with high levels of SPS, but have performed more research in 2020 in which they stated that the 5-HTTLPR s/s genotype and SPS were not significantly associated. Chen et al. (2011) have identified 10 polymorphisms, also associated with dopamine subsystems, that contribute to SPS and found that these polymorphisms account for 15% of the variance of SPS. They discuss that it is the interaction between dopamine subsystems (such as synthesis, transport and degradation, receptors and modulation) that contribute uniquely to HSPs, and that the subsystems do not function independently, but interactively and cumulatively.

As said, the 5-HTTLPR gene is associated with emotional reactivity, which is not only a feature of SPS, but also of other psychopathologies (Gonda et al., 2009). Homberg et al. (2016) have reviewed similarities between SPS and the 5-HTTLPR gene. They explain that when comparing features of the 5-HTTLPR s/s genotype and features of SPS, the aspects of DOES can often to a certain extent, depending on the feature, be supported by characteristics of the 5-HTTLPR gene. Their findings are depicted in **figure 11**, which shows that for the four facets of sensitivity (DOES), influenced by environments and following differential susceptibility, symptoms or characteristics of SPS are also found in individuals with the 5-HTTLPR s/s genotype and the 5HTT knockouts, which is the equivalent of 5-HTTLPR s/s in rodents. It also shows that there are overlapping features between SPS, neuroticism and depression in the facets of stronger emotional reactivity and susceptibility to overstimulation.

Before the 2016 article, in 2011, Homberg and Lesch had stated that because of the many crossover interactions on psychopathologies and behavioral issues regarding emotionality (Aron et al., 2012), the common genetic factors underlying higher emotionality are probably neutral. They suggest that the negative or positive behavioral outcomes related to the higher emotionality genes are shaped by an individual’s environment. The statement on common neutral genes still holds and might indeed explain the crossover interactions between traits and psychopathologies that are characterized by higher emotionality. Despite the similarities between the 5-HTTLPR s/s phenotype and SPS characteristics, further research is needed to investigate the relation between the gene and SPS, also to establish the relation between SPS and associated, 5-HTTLPR related, theories and mood disorders.



Sensitivity Facet	SPS	5-HTTLPR s-allele 5-HTT knockout
① Greater awareness of environmental subtleties	• More sensitive to other people's mood and sensitive to being observed • Stronger activation in brain regions for sensory information processing (sensory cortex) and and attention	• More sensitive to other people's mood and sensitive to being observed • Focus attention to goal-relevant information • Hyperexcitability and connectivity in sensory cortex
② Deeper processing of sensory information	• 'Pause to check' • Increased activation of brain regions involved in action planning, attention, decision making and interoceptive awareness	• Improved memory and decision making • Increased activation of brain regions involved in decision making and interoceptive awareness
③ Stronger emotional reactions	• Being more affected by violent movies • Increased activity of areas involved in empathy	• Neuroticism • Increased activity of areas involved in emotion
④ Enhanced susceptibility to overstimulation	• Need for recovery time after viewing arousing stimuli • Risk for depression	• Risk for depression • Failure to produce adequate modulation of excitatory drive under stress

Figure 11. Summary of the similarities between the SPS trait and inherited 5-HTT down-regulation in humans as well as rodents (5-HTT knockout). In childhood, exposure to adverse or supportive environmental stimuli shape 'affect' in later life for better and for worse, according to the differential susceptibility hypothesis. This affective state may bias the four sensitivity facets found both in people with SPS and inherited 5-HTT down-regulation towards either increased sensitivity to adverse environmental stimuli, or positive/rewarding environmental stimuli. The table summarizes the phenotypes and neural processes reported for each of the four facets in people with SPS and 5-HTTLPR s-allele carriers/5-HTT knockout rodents. (Homberg et al., 2016)

Inhibition-excitation balance

In the brain, integration of information is mediated through complex signaling in the synapses, which can be either excitatory (glutamate) or inhibitory (GABA) (Tatti et al., 2017). Homberg et al. (2016) showed that faster sensory processing was associated with reduced inhibitory control over excitatory neurons in the somatosensory cortex, which leads to an increase in excitation and filtering of irrelevant stimuli, which is called sensory gating (Miceli et al., 2017). Greven et al. (2019) suggest that it might be possible that the increase of excitability extends to other parts of the brain, since GABA system components are reduced not only in the somatosensory cortex, but also in the prefrontal cortex and the hippocampus, areas that have been proven to be relevant to the cardinal features of SPS. Greven et al. also discuss brain maturation, since GABA has a primarily excitatory function in the developing brain, while it has an inhibitory function in the mature brain. This inhibitory function in the brain is facilitated by chloride influx through GABA-gated chloride channels, and is dependent on chloride gradients that are established by the potassium chloride cotransporter 'KCC2' (Leonzino et al., 2016; Tanis et al., 2009). Tanis et al. (2009) found (in *C. Elegans*) that in the absence of KCC2, chloride gradients seem to be altered in neurons such that normally inhibitory signals then become excitatory. It has also been shown by Miceli et al. (2017) that in 5-HTT knockout rats the expression of KCC2 is reduced in the cortex, which would lead to an increase of membrane depolarization of postsynaptic cells that receive GABAergic input. This raises the possibility that an imbalance in KCC2 expression and/or neuronal immaturity might be related to the behavioral profile of the 5-HTT knockout rats and thus also to environmental sensitivity or SPS.

Homberg et al. (2016) also discuss the neuronal inhibitory and excitatory systems and suggest that, in line with the 5-HTTLPR knockouts, SPS seems to be associated with neural hyperexcitability in the basolateral amygdala and the sensory cortex. They support this suggestion by explaining that in the 5-HTTLPR knockouts, there is less inhibitory control and more spine density (or: more excitatory synapses). In reaction to stress, a possible adaptation of the brain is to decrease inhibitory control and increase spine density (Luscher & Fuchs, 2015; Nietzer et al., 2011). However, according to Hombergs suggestion, non-HSPs have a larger range of adaptation in their level of inhibition upon a stress response, while HSPs have a much lower range, meaning they are not able to further lower their level of inhibition in response to stress (**fig. 12**). This adaptation to stress thus is not possible for HSPs, which causes Homberg et al. to hypothesize that this impossibility to change leads to susceptibility to overstimulation and depression symptoms.

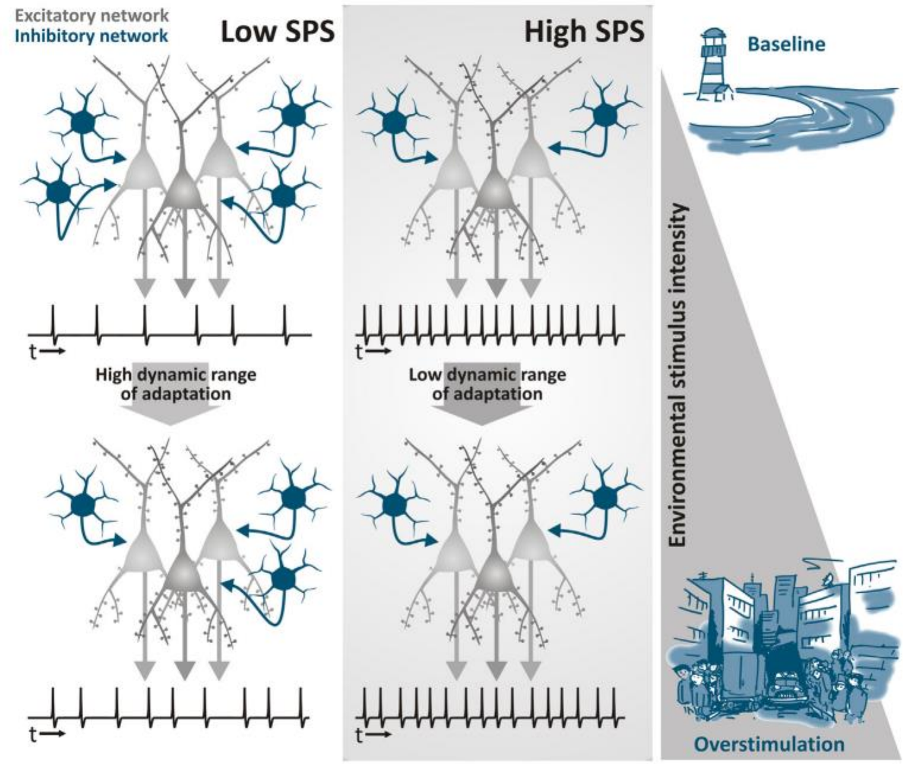


Fig 12. SPS and 5-HTTLPR knockouts are associated with neuronal hyperexcitability in e.g. the basolateral amygdala mediated by a reduction of inhibitory control and an increase of spine density. In response to stress, inhibitory control is reduced, while spine density is being increased. However, in SPS this is not possible, which is suggested to contribute to susceptibility to overstimulation.
(Homberg et al., 2016)

Hypothalamus-pituitary-adrenal axis

The hypothalamus-pituitary-adrenal (HPA) axis is implicated in the physiological responses to the environment to provide the ability to react adaptively to events. It has been associated to early life stress and environmental sensitivity (Boyce & Ellis, 2005), but no evidence has been found for associated changes in brain structures (e.g. hypothalamus and pituitary) that regulate HPA-axis activity in SPS (van der Doelen et al., 2014). However, changes in HPA-axis associated hormone and mRNA levels have been associated with 5-HTT knockout rats, as well as the influence of epigenetic mechanisms. The results on the 5-HTT knockout rats are of interest for research on the HPA-axis in SPS since they share striking similarities, as described earlier.

Van der Doelen et al. (2014) have found that 5-HTT knockout rats showed increased plasma corticosterone levels, which mediate stress response (Herman et al., 2016), under baseline conditions in comparison to wild-type rats. This was related to an increase of adrenal mRNA levels of, amongst others, the adrenocorticotropic hormone (ACTH) receptor, which is released by the pituitary and signals for production of e.g. corticosterone in the adrenal cortex (Herman et al., 2016). However, corticosterone levels in the knockout rats decreased after experiencing early life stress. Moreover, naïve 5-HTT knockout rats appeared to be more sensitive to adrenal ACTH, which is in line with the high corticosterone levels.

Furthermore, van der Doelen et al. (2014) found evidence of the influence of epigenetic mechanisms, especially DNA methylation, on environmental sensitivity. DNA methylation tends to inhibit the transcription activity of the methylated area. Van der Doelen et al. found that in the amygdala of 5-HTT knockout rats that were exposed to early life stress, there was increased DNA methylation of the corticotrophin releasing factor (CRF). CRF is released by the hypothalamus upon stress, which stimulates the release of ACTH in the pituitary (Herman et al., 2016). This finding significantly correlated with a reduction of CRF mRNA levels, which were in turn correlated with improved stress coping behavior induced by sensitivity to environments.

These results implicate that peripheral systems independent of the brain can contribute to an increase in sensitivity to the environment and that environmental factors through epigenetic mechanisms in the brain can influence HPA-axis reactivity, without directly changing functioning of the hypothalamus and pituitary. Despite the fact that there are no clear results yet on the relation between the HPA-axis mechanisms and SPS, connections that are being made between the HPA-axis, environmental sensitivity and 5-HTT knockouts are certainly interesting for future research on SPS and its underlying mechanisms.

Conclusion

Sensory Processing Sensitivity is an environmental sensitivity theory that can be described by the core aspects of Depth of processing, ease of Overstimulation, Emotional reactivity and Sensitivity to stimuli (DOES). It can be compared to the theory of differential susceptibility, which emphasizes the influence of the environment on the development of more sensitive individuals. This also holds true for HSPs, since it has been shown that a positive environment (e.g. high quality of parenting) benefits the development of skills regarding higher order cognitive processing, reflective thinking, calm and awareness, while a negative environment diminishes reward and increases chances of developing anxiety and depression. One aspect of SPS that clearly separates SPS theory from other environmental sensitivity theories is the combination of the four core aspects, with depth of processing in particular. Neuroimaging research have shown results that support higher levels of alertness and awareness, attention to detail and emotional reactivity in association with SPS. Results on depth of processing are more tentative, but evidence of brain activation in areas involved in higher order cognitive processing has been found in association with high SPS scores. Suggestions on the causes of SPS have been made in comparison to underlying mechanisms of anxiety and depression, which HSPs are prone to develop, especially in negative environments. Research has been done on the 5-HTTLPR serotonin transporter, also in association with levels of the GABA neurotransmitter and the HPA-axis. Results have shown some association with SPS, but these however are still preliminary and need further research.

Despite results seeming to support the theory of Sensory Processing Sensitivity, further research is needed to unravel underlying mechanisms and implications of this temperament trait. Interesting comparisons are found between SPS, anxiety, depression and perhaps other neuropathologies, which offers opportunities to discover shared mechanisms and solutions to behavioral difficulties. However, since SPS has its own unique facets, further neuroimaging and neurobiological research would certainly benefit the understanding of the trait. Outcomes could inform HSPs on their possible challenges and help them to strengthen their beneficial characteristics. Furthermore, results on SPS research could not only benefit HSPs, but also their environment and non-HSPs, since SPS characteristics such as reflective thinking, attention to detail and a delicate sense of others moods and intentions are certainly beneficial for e.g. employees and Human Resources, or for more personal goals such as development and growth.

References

Acevedo, B., Aron, E., Aron, A., Sangster, M., Collins, N., & Brown, L. (2014). The highly sensitive brain: An fMRI study of sensory processing sensitivity and response to others' emotions. *Brain and Behavior*, *4*(4). https://doi.org/10.1002/brb3.242

Acevedo, B., Jagiellowicz, J., Aron, E., Marhenke, R., & Aron, A. (2017). Sensory processing sensitivity and childhood quality's effects on neural responses to emotional stimuli. *Clinical Neuropsychiatry*, *14*(6), 359–373.

Acevedo, B., Santander, T., Marhenke, R., Aron, A., & Aron, E. (2021). Sensory Processing Sensitivity Predicts Individual Differences in Resting-State Functional Connectivity Associated with Depth of Processing. *Neuropsychobiology*. https://doi.org/10.1159/000513527

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *18*(3), 251–270. https://doi.org/10.1177/1073858411403316

Anteraper, S. A., Triantafyllou, C., Sawyer, A. T., Hofmann, S. G., Gabrieli, J. D., & Whitfield-Gabrieli, S. (2014). Hyper-connectivity of subcortical resting-state networks in social anxiety disorder. *Brain Connectivity*, *4*(2), 81–90. https://doi.org/10.1089/BRAIN.2013.0180

Aron, A., Ketay, S., Hedden, T., Aron, E. N., Markus, H. R., & Gabrieli, J. D. E. (2010). Temperament trait of sensory processing sensitivity moderates cultural differences in neural response. *Social Cognitive and Affective Neuroscience*, *5*(2–3), 219. https://doi.org/10.1093/SCAN/NSQ028

Aron, E., Aron, A., & Jagiellowicz, J. (2012). Sensory Processing Sensitivity: A Review in the Light of the Evolution of Biological Responsivity. *Personality and Social Psychology Review*, *16*(3), 262–282. https://doi.org/10.1177/1088868311434213

Aron, E. N. (2002). *The highly sensitive child: Helping our children thrive when the world overwhelms them* (1st ed.). Harmony.

Aron, E. N., & Aron, A. (1997). Sensory-Processing Sensitivity and Its Relation to Introversion and Emotionality. *Journal of Personality and Social Psychology*, *73*(2), 345–368. https://doi.org/10.1037/0022-3514.73.2.345

Assary, E., Zavos, H. M. S., Krapohl, E., Keers, R., & Pluess, M. (2020). Genetic architecture of Environmental Sensitivity reflects multiple heritable components: a twin study with adolescents. *Molecular Psychiatry 2020 26:9*, *26*(9), 4896–4904. https://doi.org/10.1038/S41380-020-0783-8

Babaev, O., Piletti Chatain, C., & Krueger-Burg, D. (2018). Inhibition in the amygdala anxiety circuitry. *Experimental & Molecular Medicine*, *50*(4). https://doi.org/10.1038/S12276-018-0063-8

Baumeister, R. F., Vohs, K. D., DeWall, C. N., & Zhang, L. (2007). How emotion shapes behavior: feedback, anticipation, and reflection, rather than direct causation. *Personality and Social Psychology Review : An Official Journal of the Society for Personality and Social Psychology, Inc*, *11*(2), 167–203. https://doi.org/10.1177/1088868307301033

Beevers, C. G., Marti, C. N., Lee, H. J., Stote, D. L., Ferrell, R. E., Hariri, A. R., & Telch, M. J. (2011). Associations between serotonin transporter gene promoter region (5-HTTLPR) polymorphism and gaze bias for emotional information. *Journal of Abnormal Psychology*, *120*(1), 187–197. https://doi.org/10.1037/A0022125

Belsky, J. (1997). Variation in Susceptibility to Environmental Influence: An Evolutionary Argument. *Psychological Inquiry*, *8*(3), 182–186. https://doi.org/10.1207/S15327965PLI0803_3

Belsky, J., & Pluess, M. (2009). Beyond Diathesis Stress: Differential Susceptibility to Environmental Influences. *Psychological Bulletin*, *135*(6), 885–908. https://doi.org/10.1037/A0017376

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex (New York, N.Y. : 1991)*, *19*(12), 2767–2796. https://doi.org/10.1093/CERCOR/BHP055

Booth, C., Standage, H., & Fox, E. (2015). Sensory-processing sensitivity moderates the association between childhood experiences and adult life satisfaction. *Personality and Individual Differences*, *87*, 24–29. https://doi.org/10.1016/J.PAID.2015.07.020

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, *17*(2), 271–301. https://doi.org/10.1017/S0954579405050145

Brethel-Haurwitz, K. M., O'Connell, K., Cardinale, E. M., Stoianova, M., Stoycos, S. A., Lozier, L. M., VanMeter, J. W., & Marsh, A. A. (2017). Amygdala-midbrain connectivity indicates a role for the mammalian parental care system in human altruism. *Proceedings. Biological Sciences*, *284*(1865). https://doi.org/10.1098/RSPB.2017.1731

Chen, C., Chen, C., Moyzis, R., Stern, H., He, Q., Li, H., Li, J., Zhu, B., & Dong, Q. (2011). Contributions of dopamine-related genes and environmental factors to highly sensitive personality: A multi-step neuronal system-level approach. *PLoS ONE*, *6*(7). https://doi.org/10.1371/journal.pone.0021636

Costa, P. T., & McCrae, R. R. (1992). Revised NEO Personality Inventory and NEO Five Factor Inventory professional manual. *Odessa, FL: Psychological Assessment Resources*.

de Villiers, B., Lionetti, F., & Pluess, M. (2018). Vantage sensitivity: a framework for individual differences in response to psychological intervention. *Social Psychiatry and Psychiatric Epidemiology*, *53*(6), 545–554. https://doi.org/10.1007/S00127-017-1471-0/FIGURES/1

Decety, J., & Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *13*(6), 580–593. https://doi.org/10.1177/1073858407304654

Dronkers, N. F., Wilkins, D. P., van Valin, R. D., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition*, *92*(1–2), 145–177. https://doi.org/10.1016/j.cognition.2003.11.002

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & Ijzendoorn, M. H. van. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology*, *23*(1). https://doi.org/10.1017/S0954579410000611

Gerstenberg, F. X. R. (2012). Sensory-processing sensitivity predicts performance on a visual search task followed by an increase in perceived stress. *Personality and Individual Differences*, *53*(4). https://doi.org/10.1016/j.paid.2012.04.019

Ghaziri, J., Tucholka, A., Girard, G., Boucher, O., Houde, J. C., Descoteaux, M., Obaid, S., Gilbert, G., Rouleau, I., & Nguyen, D. K. (2018). Subcortical structural connectivity of insular subregions. *Scientific Reports*, *8*(1). https://doi.org/10.1038/S41598-018-26995-0

Gonda, X., Fountoulakis, K. N., Juhasz, G., Rihmer, Z., Lazary, J., Laszik, A., Akiskal, H. S., & Bagdy, G. (2009). Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(2), 106–113. https://doi.org/10.1007/S00406-008-0842-7

Gray, J. A. (1982). Précis of The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system. *Behavioral and Brain Sciences*, *5*(3), 469–484. https://doi.org/10.1017/S0140525X00013066

Gray, J. A., & McNaughton, N. (2000). The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system. *Oxford University Press, Oxford*.

Greven, C. U., Lionetti, F., Booth, C., Aron, E. N., Fox, E., Schendan, H. E., Pluess, M., Bruining, H., Acevedo, B., Bijttebier, P., & Homberg, J. (2019). Sensory Processing Sensitivity in the context of Environmental Sensitivity: A critical review and development of research agenda. *Neuroscience and Biobehavioral Reviews*, *98*, 287–305. https://doi.org/10.1016/J.NEUBIOREV.2019.01.009

Hedden, T., Ketay, S., Aron, A., Markus, H. R., & Gabrieli, J. D. E. (2008). Cultural influences on neural substrates of attentional control. *Psychological Science*, *19*(1), 12–17. https://doi.org/10.1111/J.1467-9280.2008.02038.X

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016). Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Comprehensive Physiology*, *6*(2), 603. https://doi.org/10.1002/CPHY.C150015

Hoffmann, A., Marhenke, R., & Sachse, P. (2022). Sensory processing sensitivity predicts performance in an emotional antisaccade paradigm. *Acta Psychologica*, *222*. https://doi.org/10.1016/J.ACTPSY.2021.103463

Homberg, J. R., & Lesch, K. P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry*, *69*(6), 513–519. https://doi.org/10.1016/J.BIOPSYCH.2010.09.024

Homberg, J. R., Schubert, D., Asan, E., & Aron, E. N. (2016). Sensory processing sensitivity and serotonin gene variance: Insights into mechanisms shaping environmental sensitivity. *Neuroscience and Biobehavioral Reviews*, *71*, 472–483. https://doi.org/10.1016/J.NEUBIOREV.2016.09.029

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., & Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science (New York, N.Y.)*, *286*(5449), 2526–2528. https://doi.org/10.1126/SCIENCE.286.5449.2526

Jabbi, M., & Keysers, C. (2008). Inferior Frontal Gyrus Activity Triggers Anterior Insula Response to Emotional Facial Expressions. *Emotion*, *8*(6), 775–780. https://doi.org/10.1037/A0014194

Jagiellowicz, J., Xu, X., Aron, A., Aron, E., Cao, G., Feng, T., & Weng, X. (2011). The trait of sensory processing sensitivity and neural responses to changes in visual scenes. *Social Cognitive and Affective Neuroscience*, *6*(1), 38–47. https://doi.org/10.1093/SCAN/NSQ001

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*(7534), 284–292. https://doi.org/10.1038/NATURE14188

Jang, K. L., Livesley, W. J., & Vernon, P. A. (1996). Heritability of the big five personality dimensions and their facets: a twin study. *Journal of Personality*, *64*(3), 577–592. https://doi.org/10.1111/J.1467-6494.1996.TB00522.X

Koolhaas, J. M., Korte, S. M., de Boer, S. F., van der Vegt, B. J., van Reenen, C. G., Hopster, H., de Jong, I. C., Ruis, M. A. W., & Blokhuis, H. J. (1999). Coping styles in animals: current status in behavior and stress-physiology. *Neuroscience and Biobehavioral Reviews*, *23*(7), 925–935. https://doi.org/10.1016/S0149-7634(99)00026-3

Krall, S. C., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P. T., Eickhoff, S. B., Fink, G. R., & Konrad, K. (2015). The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. *Brain Structure & Function*, *220*(2), 587–604. https://doi.org/10.1007/S00429-014-0803-Z

Leonzino, M., Busnelli, M., Antonucci, F., Verderio, C., Mazzanti, M., & Chini, B. (2016). The Timing of the Excitatory-to-Inhibitory GABA Switch Is Regulated by the Oxytocin Receptor via KCC2. *Cell Reports*, *15*(1), 96. https://doi.org/10.1016/J.CELREP.2016.03.013

Licht, C. L., Mortensen, E. L., Hjordt, L. v., Stenbæk, D. S., Arentzen, T. E., Nørremølle, A., & Knudsen, G. M. (2020). Serotonin transporter gene (SLC6A4) variation and sensory processing sensitivity—Comparison with other anxiety-related temperamental dimensions. *Molecular Genetics & Genomic Medicine*, *8*(8), 1352. https://doi.org/10.1002/MGG3.1352

Licht, C., Mortensen, E. L., & Knudsen, G. M. (2011). Association between sensory processing sensitivity and the serotonin transporter polymorphism 5-HTTLPR short/short genotype. *Biological Psychiatry*, *69*.

Lionetti, F., Aron, A., Aron, E. N., Burns, G. L., Jagiellowicz, J., & Pluess, M. (2018). Dandelions, tulips and orchids: evidence for the existence of low-sensitive, medium-sensitive and high-sensitive individuals. *Translational Psychiatry 2018 8:1*, *8*(1), 1–11. https://doi.org/10.1038/S41398-017-0090-6

Liss, M., Timmel, L., Baxley, K., & Killingsworth, P. (2005). Sensory processing sensitivity and its relation to parental bonding, anxiety, and depression. *Personality and Individual Differences*, *39*(8), 1429–1439. https://doi.org/10.1016/J.PAID.2005.05.007

Luscher, B., & Fuchs, T. (2015). GABAergic control of depression-related brain states. *Advances in Pharmacology (San Diego, Calif.)*, *73*, 97–144. https://doi.org/10.1016/BS.APHA.2014.11.003

Malinakova, K., Novak, L., Trnka, R., & Tavel, P. (2021). Sensory Processing Sensitivity Questionnaire: A Psychometric Evaluation and Associations with Experiencing the COVID-19 Pandemic. *International Journal of Environmental Research and Public Health*, *18*(24). https://doi.org/10.3390/IJERPH182412962

Miceli, S., Kasri, N. N., Joosten, J., Huang, C., Kepser, L., Proville, R., Selten, M. M., van Eijs, F., Azarfar, A., Homberg, J. R., Celikel, T., & Schubert, D. (2017). Reduced Inhibition within Layer IV of Sert Knockout Rat Barrel Cortex is Associated with Faster Sensory Integration. *Cerebral Cortex*, *27*(2), 933–949. https://doi.org/10.1093/CERCOR/BHX016

Moore, S. R., & Depue, R. A. (2016). Neurobehavioral foundation of environmental reactivity. *Psychological Bulletin*, *142*(2). https://doi.org/10.1037/bul0000028

Murphy, D. L., Lerner, A., Rudnick, G., & Lesch, K. P. (2004). Serotonin transporter: gene, genetic disorders, and pharmacogenetics. *Molecular Interventions*, *4*(2), 109–123. https://doi.org/10.1124/MI.4.2.8

Nietzer, S. L., Bonn, M., Jansen, F., Heiming, R. S., Lewejohann, L., Sachser, N., Asan, E. S., Lesch, K. P., & Schmitt, A. G. (2011). Serotonin transporter knockout and repeated social defeat stress: impact on neuronal morphology and plasticity in limbic brain areas. *Behavioural Brain Research*, *220*(1), 42–54. https://doi.org/10.1016/J.BBR.2011.01.011

Nocentini, A., Menesini, E., & Pluess, M. (2018). The Personality Trait of Environmental Sensitivity Predicts Children's Positive Response to School-Based Antibullying Intervention. *Clinical Psychological Science*, *6*(6), 848–859. https://doi.org/10.1177/2167702618782194/ASSET/IMAGES/LARGE/10.1177_2167702618782194-FIG2.JPEG

Pearson, R., McGeary, J. E., Maddox, W. T., & Beevers, C. G. (2016). Serotonin promoter polymorphism (5-HTTLPR) predicts biased attention for emotion stimuli: Preliminary evidence of moderation by the social environment. *Clinical Psychological Science*, *4*(1), 122–128. https://doi.org/10.1177/2167702614562470/ASSET/IMAGES/LARGE/10.1177_2167702614562470-FIG2.JPEG

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, *54*(5), 504–514. https://doi.org/10.1016/S0006-3223(03)00168-9

Pluess, M. (2015). Individual Differences in Environmental Sensitivity. *Child Development Perspectives*, *9*(3), 138–143. https://doi.org/10.1111/CDEP.12120

Pluess, M. (2017). Vantage Sensitivity: Environmental Sensitivity to Positive Experiences as a Function of Genetic Differences. *Journal of Personality*, *85*(1), 38–50. https://doi.org/10.1111/JOPY.12218

Pluess, M., Assary, E., Lionetti, F., Lester, K. J., Krapohl, E., Aron, E. N., & Aron, A. (2018). Environmental sensitivity in children: Development of the highly sensitive child scale and identification of sensitivity groups. *Developmental Psychology*, *54*(1), 51–70. https://doi.org/10.1037/DEV0000406

Pluess, M., & Boniwell, I. (2015a). Sensory-Processing Sensitivity predicts treatment response to a school-based depression prevention program: Evidence of Vantage Sensitivity. *Personality and Individual Differences*, *82*, 40–45. https://doi.org/10.1016/J.PAID.2015.03.011

Pluess, M., & Boniwell, I. (2015b). Sensory-Processing Sensitivity predicts treatment response to a school-based depression prevention program: Evidence of Vantage Sensitivity. *Personality and Individual Differences*, *82*, 40–45. https://doi.org/10.1016/J.PAID.2015.03.011

Rajmohan, V., & Mohandas, E. (2007). Mirror neuron system. *Indian Journal of Psychiatry*, *49*(1), 66. https://doi.org/10.4103/0019-5545.31522

Ren, Y., Nguyen, V. T., Sonkusare, S., Lv, J., Pang, T., Guo, L., Eickhoff, S. B., Breakspear, M., & Guo, C. C. (2018). Effective connectivity of the anterior hippocampus predicts recollection confidence during natural memory retrieval. *Nature Communications*, *9*(1). https://doi.org/10.1038/S41467-018-07325-4

Saxe, R., & Powell, L. J. (2006). It's the thought that counts: specific brain regions for one component of theory of mind. *Psychological Science*, *17*(8), 692–699. https://doi.org/10.1111/J.1467-9280.2006.01768.X

Schilbach, L., Bzdok, D., Timmermans, B., Fox, P. T., Laird, A. R., Vogeley, K., & Eickhoff, S. B. (2012). Introspective Minds: Using ALE Meta-Analyses to Study Commonalities in the Neural Correlates of Emotional Processing, Social & Unconstrained Cognition. *PLOS ONE*, *7*(2), e30920. https://doi.org/10.1371/JOURNAL.PONE.0030920

Schimitel, F. G., de Almeida, G. M., Pitol, D. N., Armini, R. S., Tufik, S., & Schenberg, L. C. (2012). Evidence of a suffocation alarm system within the periaqueductal gray matter of the rat. *Neuroscience*, *200*, 59–73. https://doi.org/10.1016/J.NEUROSCIENCE.2011.10.032

Schipper, P., Hiemstra, M., Bosch, K., Nieuwenhuis, D., Adinolfi, A., Glotzbach, S., Borghans, B., Lopresto, D., Fernández, G., Klumpers, F., Hermans, E. J., Roelofs, K., Henckens, M. J. A. G., & Homberg, J. R. (2019). The association between serotonin transporter availability and the neural correlates of fear bradycardia. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(51), 25941–25947. https://doi.org/10.1073/PNAS.1904843116

Schjolden, J., & Winberg, S. (2007). Genetically determined variation in stress responsiveness in rainbow trout: Behavior and neurobiology. *Brain, Behavior and Evolution*, *70*(4), 227–238. https://doi.org/10.1159/000105486

Schwabe, L., & Wolf, O. T. (2013). Stress and multiple memory systems: from "thinking" to "doing." *Trends in Cognitive Sciences*, *17*(2), 60. https://doi.org/10.1016/J.TICS.2012.12.001

Smolewska, K. A., Mccabe, S. B., & Woody, E. Z. (2006). *A psychometric evaluation of the Highly Sensitive Person Scale: The components of sensory-processing sensitivity and their relation to the BIS/BAS and "'Big Five.'"* https://doi.org/10.1016/j.paid.2005.09.022

Spreng, R. N., Mar, R. A., & Kim, A. S. N. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *Journal of Cognitive Neuroscience*, *21*(3), 489–510. https://doi.org/10.1162/JOCN.2008.21029

Suomi, S. J. (1997). Early determinants of behaviour: evidence from primate studies. *British Medical Bulletin*, *53*(1), 170–184. https://doi.org/10.1093/OXFORDJOURNALS.BMB.A011598

Tanis, J. E., Bellemer, A., Moresco, J. J., Forbush, B., & Koelle, M. R. (2009). The Potassium Chloride Cotransporter KCC-2 Coordinates Development of Inhibitory Neurotransmission and Synapse Structure in Caenorhabditis elegans. *The Journal of Neuroscience*, *29*(32), 9943. https://doi.org/10.1523/JNEUROSCI.1989-09.2009

Tatti, R., Haley, M. S., Swanson, O. K., Tselha, T., & Maffei, A. (2017). Neurophysiology and Regulation of the Balance Between Excitation and Inhibition in Neocortical Circuits. *Biological Psychiatry*, *81*(10), 821–831. https://doi.org/10.1016/J.BIOPSYCH.2016.09.017

Ujiie, Y., & Takahashi, K. (2022). Subjective Sensitivity to Exteroceptive and Interoceptive processing in Highly Sensitive Person. *Psychological Reports*, *2022*(0), 1–17. https://doi.org/10.1177/00332941221119403/FORMAT/EPUB

Utevsky, A. v., Smith, D. v., & Huettel, S. A. (2014). Precuneus Is a Functional Core of the Default-Mode Network. *The Journal of Neuroscience*, *34*(3), 932. https://doi.org/10.1523/JNEUROSCI.4227-13.2014

van der Doelen, R. H. A., Deschamps, W., D'Annibale, C., Peeters, D., Wevers, R. A., Zelena, D., Homberg, J. R., & Kozicz, T. (2014). Early life adversity and serotonin transporter gene variation interact at the level of the adrenal gland to affect the adult hypothalamo-pituitary-adrenal axis. *Translational Psychiatry 2014 4:7*, *4*(7), e409–e409. https://doi.org/10.1038/TP.2014.57

van Overwalle, F., & Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *NeuroImage*, *48*(3), 564–584. https://doi.org/10.1016/J.NEUROIMAGE.2009.06.009

Wilson, D. S., Coleman, K., Clark, A. B., & Biederman, L. (1993). Shy-bold continuum in pumpkinseed sunfish (Lepomis gibbosus): an ecological study of a psychological trait. *Journal of Comparative Psychology*, *107*(3), 250–260. https://doi.org/10.1037/0735-7036.107.3.250

Appendix

Highly Sensitive Person Scale Items – Aron 1997

1. Are you easily overwhelmed by strong sensory input?
2. Do you seem to be aware of subtleties in your environment?
3. Do other people's moods affect you?
4. Do you tend to be more sensitive to pain?
5. Do you find yourself needing to withdraw during busy days into bed or into a darkened room or any place where you can have some privacy and relief from stimulation?
6. Are you particularly sensitive to the effects of caffeine?
7. Are you easily overwhelmed by things like bright lights, strong smells, coarse fabrics or sirens close by?
8. Do you have a rich, complex inner life?
9. Are you made uncomfortable by loud noises?
10. Are you deeply moved by the arts or music?
11. Does your nervous system sometimes feel so frazzled that you just have to get off by yourself?
12. Are you conscientious?
13. Do you startle easily?
14. Do you get rattled when you have a lot to do in a short amount of time?
15. When people are uncomfortable in a physical environment do you tend to know what needs to be done to make it more comfortable (like changing the lightning or the seating)?
16. Are you annoyed when people try to get you to do too many things at once?
17. Do you try hard to avoid making mistakes or forgetting things?
18. Do you make it a point to avoid violent movies and TV shows?
19. Do you become unpleasantly aroused when a lot is going on around you?
20. Does being very hungry create a strong reaction in you, disrupting your concentration or mood?
21. Do changes in your life shake you up>
22. Do you notice and enjoy delicate or fine scents, tastes, sounds, works of art?
23. Do you find it unpleasant to have a lot going on at once?
24. Do you make it a high priority to arrange your life to avoid upsetting or overwhelming situations?
25. Are you bothered by intense stimuli, like loud noises or chaotic scenes?
26. When you must compete or be observed while performing a task, do you become so nervous or shaky that you do much worse than you would otherwise?
27. When you were a child, did parents or teachers seem to see you as sensitive or shy?