Shutdown States and Stress Instability in Autism*

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ABSTRACT

In a young, high functioning autistic child we have observed a particular sequence of behavior (stress response) culminating in an involuntary state of unresponsiveness, immobility, sleepiness, and limpness to the touch, which we call "shutdown" (SD). The stress response is triggered by a social performance expectation, as in school settings or interactions with others, and it escalates as an adult continues to pressure the child to respond to a task she perceives as difficult. Attempts at understanding SD have lead us to recognize a feature of the human nervous system, coined "stress instability" (SI). The instability comprises dynamics wherein the stress and anxiety caused by anticipated or perceived social inadequacy has a numbing effect on the mind that, in turn, causes a further depression of social performance. The repeating sequence of influences and consequences becomes a vicious circle in which the quality of social performance progressively deteriorates to a level far below the individual's capability. The basolateral amygdala (BLA) is identified as playing a dominant role in SI through its response to corticotropin releasing factor (CRF). The hyperreactivity of the BLA, and therefore the severity of SI, can be diminished in principle by regulating the activity of the CRF receptors CRFR1 and CRFR2 through CRFR1 antagonists or CRFR2 agonists. The severity of SI can also be decreased simply by avoiding excessive stress for an extended period. We posit that SD is brought on by SI and that it constitutes a recovery from the accumulated stress. In young children, frequent SI-SD episodes result in nervous system damage and developmental impairments of a kind seen in the autistic spectrum. Even if the child is already predisposed to autism, SI-SD episodes make things worse, and should therefore be avoided. We propose an approach to intervention through which this can be accomplished and that has proven effective for the child mentioned above. We emphasize the merit of early detection of shyness as a sign of hypersensitivity to social stress that can give rise to SI. Our explorations suggest that SD may be common among autistics to the point of defining a subtype within the autistic spectrum.

INTRODUCTION

In a child diagnosed as high-functioning within the autistic spectrum, peculiar states have been observed wherein the child was unresponsive, sleepy, immobile, and limp to the touch for several minutes, and then fell asleep in a chair for as briefly as 10 minutes and up to 2 hours. These "shutdown" (SD) states were always triggered by an ongoing social stress of a certain kind, and they developed with increasing severity and frequency over a period of about a year. During this time the child developed fears, sleep disturbances, became more rigid, socially withdrawn and emotional, and had difficulty remembering previously mastered academics. Faced with these developments, a project was started in which we attempted to understand the physiology of SD states and their triggers. In reporting on this project, we emphasize that our work is based on observations of a single 6-year-old child, referred to as "the SD child". However, the notions developed and discussed are expected to have a wider applicability.

DESCRIPTION OF SHUTDOWNS

Shutdowns in academic settings

We observed the SD child during Kindergarten-level academic lessons taught by the child's mother over a period of 10 weeks, 5 days each week. The sessions lasted approximately 1 hour with 2 breaks. Each session consisted of 3 subjects. The child and teacher were alone in a small room together, seated side by side at a desk. Each lesson was presented for 2-5 minutes followed by a task to reinforce the lesson such as copying letters or identifying a rhyming word. The goal was to work for 15 minutes on a subject before having a 5-10 minute break consisting of a fun motor activity chosen ahead of time by the child. Under no circumstances was the child allowed to avoid a task. She was required to finish it, even if long rest breaks were taken. A visual schedule was in view of the child with symbols depicting the order in which the subjects and breaks would occur. The teacher offered help as needed. Since the goal was to reduce the number of shutdowns and to increase the length of time she could stay on task without a stress response, reinforcement approaches were varied as needed.

Progression of the stress response and shutdown

In general, the child demonstrated a very low threshold for frustration and a reluctance to ask for help. The sequence of behavior described herein was repeated on many occasions and a pattern became apparent**.** When a task was difficult, the SD child looked away from the work area and became distracted. She also did this after being corrected for a mistake, such as making a letter incorrectly.

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*Available at www.cuewave.com/tau/SI-SDinAutism.pdf.
A parent version of this paper entitled "Shutdowns and Stress in Autism" is available at www.shutdownsandstressinautism.com/ StressinAutism.pdf.

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When the child was redirected back to the task, attention suffered and she rubbed her eyes and kept them closed. When further attempts to redirect were made, the child became less verbally responsive, keeping her eyes closed. In order to test if the child was attempting to "escape" the task, an enticing reward in the form of a large toy was offered for finishing the task. She attempted to return to task but seemed disoriented, did not know what the task was, and could not attend long enough to complete even a portion of it. The child expressed great interest in the toy reward, but she seemed *incapable* of finishing the task. The pencil fell from the child's hand, she slumped into the chair and complained about being tired and "needing" to sleep. If prompted again and reminded of the reward she would say "I have to sleep ". The teacher's attempts to rouse the child by touch had no effect. The child's hand was limp to the touch and she did not respond. She remained conscious but extremely reluctant to respond physically or verbally. The child then fell asleep in the chair. She was observed sleeping in the chair for as little as 10 minutes and up to 2 hours. When the child awoke, the task was completed but she was prone to shutdowns for the rest of the session.

If shutdowns occurred on 3 consecutive days, the child seemed prone to them for up to 3 weeks. With creative teaching approaches the child was able to avoid shutdowns, work at difficult tasks for a longer duration, and work for up to one hour without a break.

Stress reactions in nonacademic settings

Stress reactions have also been observed in non-academic settings including but not limited to: Meeting strangers, greeting friends and family during home visits, participating in play-dates with several other children, conversations with adults when the child was asked to recall what she did or what she liked about a recent event, play sessions in which a sibling pressed the SD child to participate in particular play themes. During these incidents the child was not pressed to respond once she indicated resistance to doing so. Thus, the stress reactions did not reach the level of shutdown.

Triggers for stress reactions and shutdowns

The escalating stress response leading to shutdown commonly occurred when the SD child was pressed by an adult to continue working on a difficult academic task requiring a verbal response. Thus the trigger was not a single event but a series of exchanges between the child and the adult which took at a few minutes. We never observed a stress response when the child played alone, interacted with animals, machines, objects or played challenging computer games. We therefore believe the child suffers a form of performance anxiety akin to stage fright, in addition to language and memory impairments that make certain tasks difficult for her.

We identified eye rubbing as the threshold stress reaction in the SD child. Once she rubbed her eyes, the stress reaction quickly escalated to a shutdown if the adult continued to press her and she was not given an opportunity to rest for a few minutes before resuming the task.

We found a hierarchy of difficulty consistent with the work of Volkmar & Cohen [1] in which tasks requiring a verbal response to a verbal question elicited the quickest stress response (e.g., "What rhymes with hat?") [1]. The more visual the task, the less stress the SD child exhibited. This pattern is what one would expect from a child with language difficulties and performance anxiety.

Avoidance behavior or involuntary response?

Is the stress response escalating to shutdown driven by physiology, or is it learned avoidance behavior? It may be a combination of both. Although one can not be sure exactly where to draw the line between intentional and unintentional acts, we believe the shutdown is driven more by physiology than by learning for several reasons: First, we have seen the SD child exhibit frank refusal behavior in academic settings. She folds her arms across her chest, turns her back to the instructor and declares that she will not do the task. Although not disruptive, destructive or violent, this behavior is more in line with the avoidance behavior described in the literature [2,3,4].This is a marked contrast to the stress reaction leading to shutdowns which can be characterized as extreme passivity. The stress response in the SD child also escalates over a few minutes, culminating in a shutdown. We have not seen a pattern such as this described in our review of the literature.

Second, the SD child exhibits limpness followed by sleep which is real and not feigned. It is difficult to imagine a child could sleep at will under these circumstances.

Finally, we observed that no amount of enticement could bring the SD child around enough for her to continue working on the task. This child was highly motivated to earn the particular toys that were offered as a reward for finishing the task. That the child attempted to finish the task but was unable to leads us to believe that she was simply overcome by the need to rest, and that the need to rest was greater than the desire for the toy. These observations lead us to believe that the progression from stress reaction to shutdown is not adequately explained as learned avoidance behavior.

STRESS INSTABILITY

In social settings, the stress and anxiety of anticipated or perceived inadequacy may bring on a mental dullness that blunts social performance. The resulting increase of stress then causes a deepening of the dullness and a further slippage of social performance. This vicious circle of increasing stress and further deterioration of social function involves an instability of sorts, here called "stress instability". It is easy to see that stress instability contributes to the development of the introvert or shy personality and that it may give rise to social phobia. In children, severe chronic stress instability can lead to shutdown episodes, and cause nervous system damage and developmental impairments within the autistic spectrum.

Stress Instability parameters

Corticotropin releasing factor (CRF) plays a dominant role as a neurotransmitter early on in the flow of stress data. CRF-mediated activity is chosen here as a measure of stress to express the instability in a simplified way. A conceptual graph of the CRF-mediated activity in

response to a social stressor, depicting both stable and unstable stress dynamics, is shown in Fig.1.

Stress instability (SI) may be characterized by three parameters: the instability growth rate, instability run up, and perseveration. The growth rate pertains to the early part (c) of the response function, immediately after the onset of the instability that occurs when the social stressor is first applied. In region (c), the response function perturbation due to the instability changes exponentially with the product *rt*, where *t* is the time, and the constant *r* is the growth rate. In terms of the perturbation doubling time *T*, one has $r = 0.693/T$. For positive *r* the stress dynamics is unstable, and the instability is worse the greater the value of *r*. For $r = 0$,

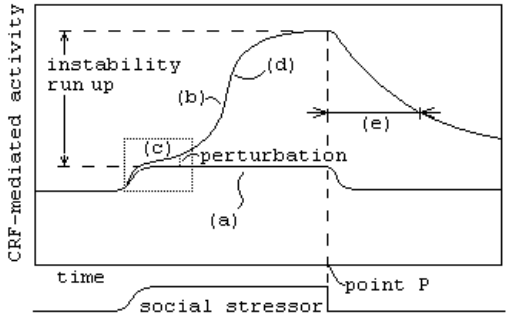


Fig. 1. Stress instability

(a) Stable stress dynamics (normal stress reaction)
(b) Unstable stress dynamics (abnormal stress reaction)
(c) Region where perturbation due to instability is determined by the growth rate
(d) Onset of physiological limiting
(e) Perseveration, defined as decline half time

Point P denotes time when the social stressor stops.

the stress dynamics is stable, and one has the normal response shown as graph (a).

In the unstable case (b), the CRF-mediated activity keeps increasing at an accelerated rate, until physiological limiting sets in near (d). Eventually, the activity settles at a level that is characterized by the "instability run up" indicated in the figure. The run up is a measure of the abnormal stress reaction.

When the social stressor ceases (at point P of the figure), the stress dynamics enters a recovery regime, wherein the CRF-mediated activity declines slowly on its return to homeostasis. The duration of the decline is characterized by its halving time, here called perseveration. Note that the use of this wording is at variance with some of the autism literature.

How can stress impair social function?

The concept of stress instability (SI) relies on the existence of a physiological mechanism which impairs social function through stress or anxiety generated by a performance expectation. That such a mechanism exists in the human nervous system is amply demonstrated by the phenomenon of stage fright. The condition, also known as debilitating performance anxiety, is estimated to afflict 2% of the US population [5].

Three aspects of the stress-driven social function impairment may serve as criteria for screening physiological mechanisms that could cause the impairment: First, the mechanism must have a graded response because various degrees of severity are observed in its manifestation. Second, the mechanism must respond quickly to an increase of stress, since people can rapidly become flustered by social embarrassment. Third, the impairment brought on by the mechanism lingers for a while after the applied external stress has ceased. With these criteria in hand we explore whether the stress-driven social impairment mechanism can possibly involve glucocorticoids, GABA, or endogenous opioids in an essential manner.

Glucocorticoids are known to affect memory consolidation and retrieval [6,7]. Such retrieval is pertinent to the impairment mechanism under discussion, since it is part and parcel of the cognitive processes involved in social functioning. High levels of circulating glucocorticoids are expected through the activation of the hypothalamus-pituitary-adrenal (HPA) axis in response to the elevated stress that is present in situations involving SI. Impairment of memory retrieval by glucocorticoids has been seen [6], but the process is much too slow to qualify as a pertinent mechanism. Specifically, it has been reported that peripheral injections of stress doses of corticosterone cause hippocampal firing rates to decrease, but only after a delay of 30 to 60 minutes [6].

Turning to neurotransmitter-mediated processes, the lingering feature favors second messenger mechanisms over the brief ligand-mediated direct gating. Second messenger mechanisms are activated by G-protein coupled receptors that are sensitive to ambient neurotransmitters, and provide hyperpolarizing leakage currents that depress the neuron spiking frequency in a semi-tonic manner. There is concern whether the initiation of this inhibitory effect occurs fast enough to pass the quick onset test.

GABA has been seen to influence learning and memory processes in mice [8]. GABA(B) receptors are G-protein coupled, as are those GABA(A) receptors that carry an alpha5 subunit. In hippocampal pyramidal neurons, the tonic inhibitory effect of the latter-type receptors has been reported as possibly affecting memory processes [9]. Since a GABA(B) blocker has improved the cognitive performance of mice, rats, and rhesus monkeys [10], one expects that GABA can impair cognition.

Opioid receptors also are coupled to G-proteins, and are known to exist in the prefrontal cortex [11,12], the site of cognitive processing. Among the endogenous opioids, beta-endorphin (BE) is a prime suspect for involvement in the social function impairment, because of its potency as an analgesic and sedative. This raises the question whether a BE-driven mechanism would involve circulating or central BE. There are two counts against the former case. First, circulating BE crosses the blood-brain barrier only slowly [13], which raises problems of speed and adequacy of central BE concentration build up. The second objection relies on the requirement that the social function impairment in response to increasing stress must be graded. The concentration of circulating BE in response to stress is somewhat graded, but the anterior pituitary releases BE into

the blood stream in squirts, so that the grading is too coarse to be satisfactory in the context of SI. Investigation of an endogenous opioid-based mechanism for the stress-driven social function impairment can benefit from the literature on opiate abuse.

The cursory exploration discussed above leaves both GABA and BE as candidates for possible involvement in the impairment mechanism. The contribution of the mechanism to the growth rate is here called the social function sensitivity to stress. This sensitivity varies from person to person and may depend on past experiences and thoughts, as well as on the state of the autonomic nervous system and the endocrine system.

PHYSIOLOGY RELATED TO STRESS INSTABILITY PARAMETERS

The basolateral amygdala affects the growth rate

The run up and perseveration are important parameters of stress instability, but the growth rate is fundamental because it determines the run up, jointly with the limiting mechanisms. For a fixed social function sensitivity to stress, the instability growth rate depends on the reactivity of circuits in the neural substrates that process stress data. Among these, the basolateral amygdala (BLA) is of particular interest since it has a variable reactivity that depends on the history of extracellular CRF. The plastically variable reactivity has been seen in rats [14], through injections into the BLA of urocortin, which is a potent CRF receptor agonist. After 5 daily injections of nonanxiety-inducing doses, the rats developed anxiety-type responses that lasted for several weeks. This is consistent with the shutdown behavior observed in the SD child, in that a shutdown raises the susceptibility to future shutdowns for several days. Repeated shutdowns on consecutive days raise susceptibility for up to three weeks.

The plastic hyperreactivity of the BLA is attributed to an increased activity of the type 1 CRF receptor CRFR1. It is therefore expected that the instability growth rate can be lowered through the action of CRFR1 antagonists such as R121919 [15].

What is crucial is that the hyperreactivity of the BLA may be *reversed*, and thus the instability growth rate reduced, by avoiding excessive stress over time. Since most educational programs for autistic children focus on "working through" stressful situations rather than on minimizing stress, this information offers a unique avenue for intervention which has proven effective in the SD child.

The basolateral amygdala limits the instability run up

The BLA features a mechanism for curbing the effect of excessive CRF concentrations, thereby reducing the instability run up. The mechanism involves a second type of CRF receptor, CRFR2, which has been reported [16,17] to have a much smaller affinity than CRFR1, and which may have an anxiolytic effect [17,18]. The different affinities of the two types of receptor results in preferential CRFR1 activation for small CRF concentrations, whereas at larger concentrations saturation of the CRFR1 receptors leads to an increasing impact of CRFR2 activity. Excitatory CRFR1 action and inhibitory CRFR2 action would then provide the mentioned curbing. Other curbs, due to capacity of chemical store, axonal transport, etc., may contribute to the physiological limiting illustrated in Fig.1 but are beyond our control, whereas the CRFR2 limiting may perhaps be manipulated. For instance, the instability run up could be decreased through a CRFR2 agonist. As compared with the CRFR1 receptor, CRFR2 is found at far fewer sites in the human body. Besides CRF, urocortin II and III have been suggested as possibly important for dampening stress sensitivity by binding to CRFR2 [19].

Beta-endorphin may increase run up and slow CRF return to homeostasis

After the social stressor ceases, central free CRF remains elevated for some time, causing a lingering of stress-related activity, as illustrated in Fig. 1 and characterized by the perseveration. At some time during the lingering, the stress-level release of central CRF will stop, but it will take time for the free CRF level to return to homeostasis. Meanwhile, the CRF can still have consequences for downstream circuitry for a time span characterized by the perseveration**.**

It turns out that this parameter can be influenced by the joint action of CRF and BE. Free CRF is removed from the brain by a unidirectional active transport, which can be modulated by certain compounds [20]. Injection of 1 nmol of BE into the lateral ventricle of mice increased the source-free CRF disappearance half time from 15 min to 60 min [20]. If central BE indeed plays a role in SI, this modulation would lengthen the perseveration and boost peak CRF levels.

We have explored this effect by calculating the course of free CRF concentration that results from the release of CRF at uniform rate for a given duration. Four cases are considered, comprising the combinations of two CRF release durations, 20 min and 40 min, and two values for the source-free CRF disappearance half time, 15 min and 60 min, that correspond to the experimental conditions [20] mentioned above. APPENDIX I shows the simple mathematical model used for the calculations. Graphs for the resulting free CRF concentrations as function of time are drawn in Fig. 2. The solid and dashed lines are for 20 min and 40 min of CRF release respectively. The results shown are for cases with source-free CRF disappearance half time, T = 15 min that occurs without BE, and T = 60 min, for the case with BE injected at the mentioned dose. The graphs demonstrate that increasing the zero-source CRF disappearance half time T not only stretches the CRF decline that occurs after attaining the maximum, but gives a larger maximum as well. Furthermore, the longer CRF release results in a larger maximum, and CRF levels remain high for a longer time. Both these effects are aggravated by the presence of BE. This result suggests that shutdowns may be prevented by breaking up a stressful session into several parts that are well separated in time.

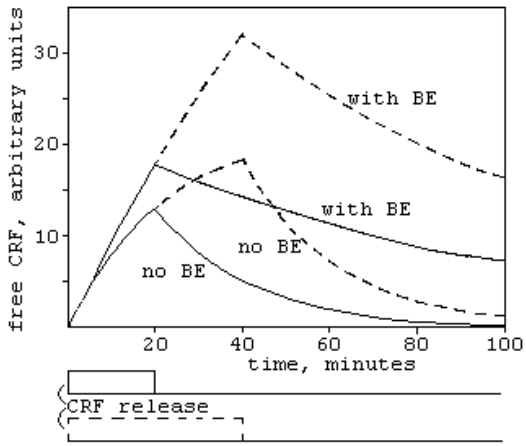
SEVERE STRESS INSTABILITY CAN LEAD TO SHUTDOWN

SD appears to be preceded by SI

Shutdown episodes in the SD child were always preceded by a stressful social event. These events all involved a performance expectation, such as home

schooling. As pressure for performance continued to be applied, the SD child became more stressed, sedated, and socially impaired, all features of SI. When, upon onset of a shutdown, the social pressure was halted, the SD child entered the dynamic regime characterized herein as perseveration. Thus, we have come to see the shutdown state as the consequence of a severe SI, wherein the child recovers from the stressful state.

The initial conditions of SD are then those prevailing in SI at point P in Fig. 1, where the instability has run its course, and the social stress has stopped. At that point, there is excessive central CRF-mediated activity, and the HPA axis has been activated, so that the levels of circulating ACTH, BE, and glucocorticoids are elevated.



If central BE is postulated to play a role in the social impairment mechanism in SI, then for consistency one must assume elevated central BE at the onset P of the shutdown state. The discussion associated with Fig. 2 would then apply, and one expects excessive CRF levels together with a long perseveration; of course, details depend on the actual concentration of central BE. The observed extended lingering of shutdowns indirectly supports the notion that elevated central BE occurs in SD.

Of course, not all episodes of stress instability lead to shutdown. For a child with small instability growth rate, or when the social stressor is of low intensity or short duration, the instability run up will be small, so that the nervous system can cope with the stress reaction without going into SD. It should also be noted that, in adolescents and even more so in adults, the consequences of SI are generally less severe than in young children. The reasons for this are related to the size of the memory store, the average emotional quality of memories, and the developmental state of the brain, particularly the amygdala and hippocampus**.** In normally developing children the amygdala increases substantially in size from 7.5 to 18.5 years of age [53]. Autistic children were seen to have enlarged bilateral amygdala in the age group from 7.5 to 12.5 years, but not from 12.75 to 18.5 years of age [53].

Hypotonia

Limpness to the touch is seen in the SD child for a short time at the beginning of shutdown episodes. This conspicuous symptom provides an important diagnostic in its own right, and it may become useful in future investigations of the SD state. Severe hypotonia has been seen in two autistic children with abnormal chromosome 15 [21,22], and hypotonia has strongly correlated with abnormal auditory brainstem responses in a set of 24 autistic children [23].

Since the hypotonia observed in the SD child is rather brief and is seen only in the stressful SD episodes, the condition may perhaps be related to cataplexy, the loss of skeletal muscle tone while conscious, which occurs in narcolepsy and is usually triggered by sudden strong emotions. [24]. Cataplexy is related to the skeletal muscle atonia that occurs during REM sleep, and that keeps us from physically enacting our dreams. This atonia is mediated by the dorsolateral pontine inhibitory area (PIA) and the medial medullary recticular formation [25]. In unanesthezised, decerebrated cats, injection of CRF into precisely selected points in the PIA and nucleus magnocellularis produced a dose-dependent suppression of muscle tone [25]. Further work on cataplexy has been done on narcoleptic dogs, showing that, during cataplexy attacks, usually active nuclei in the medial pontine recticular area are inactive [26], while certain neurons in the medial medulla have elevated activity [27].

Fig. 2. Concentration of free central CRF as function of time for different durations of CRF release, with and without the presence of central BE.

CRF = corticotropin-releasing factor
BE = beta-endorphin

The work on cataplexy is mentioned here not only for its possible connections to the limpness seen in SD, but also because several diagnostic methods, such as electromyogram (EMG) and electrooculogram (EOG) may be applicable in diagnosis and research on SD.

DAMAGE MECHANISMS

Frequent shutdowns signal conditions of extreme stress

Since states of elevated stress develop as a result of stress instability, and shutdowns are seen as resulting from severe SI, frequent shutdowns signal the existence of chronic severe stress conditions. Such conditions may cause damage to the CNS and delays in mental development. We see three damage mechanisms: the effect of elevated cortisol on the consolidation of memories, possible kindling by chronic excessive central BE and CRF, and hippocampal damage by chronically elevated glucocorticoids.

Stress levels of cortisol enhance consolidation of emotional memories

The consolidation of emotionally-laden memories is mediated by the BLA [6,7]. Of interest here is the finding that stress-levels of cortisol enhance such memories [28]. This means that both the sensation of debilitating stress, and the often negative reactions of others, are selectively remembered more keenly the next time a similar social occasion arises. The recall of such emotionally negative and painful memories adds to anxiety, and thereby increases the stress before and during the social occasion. The stress-driven mechanism of social function impairment then tends to cause a further deterioration of performance as compared with the previous unsatisfactory performance, and we see another vicious circle, now on the longer time scale that leads from one stressful social event to the next. For frequent SI-SD episodes, this "long loop" contributes to chronical hyperreactivity of the BLA.

Chronic excessive central BE and CRF can cause kindling

Since we will connect to autism, it is pertinent in the discussion of damage mechanisms to consider possible kindling effects. Among 50 children with symptoms within the autistic spectrum disorder (ASD) who had a normal early development followed by autistic regression between 2 and 3 years of age, 82% showed epileptiform activity during slow-wave sleep, as measured with magnetoencephalography (MEG) [29]. MEG is more sensitive than EEG in detecting epileptiform activity, and only 30% of the 50 ASD children had been diagnosed with clinical seizure disorder [29].

What causes the epileptiform activity that is so prevalent in autistic children? Kindling effects leading to generalized convulsions have been reported for small doses of BE or Met-enkephalin injected repeatedly into the hippocampus or posterior amygdala of rats [30]. Limbic epileptiform activity has been elicited in rats by intraventricular injection of BE in doses that do not result in analgesic or behavior signs [31].

Besides BE, excessive central CRF also has been implicated as inducing kindling. Elevated expression of the CRF receptor CRFR1, but not for CRFR2, has been found in cortical tissue obtained from 6 children with generalized epilepsy [33]. In the developing human brain, severe age-dependent seizures have been induced in vivo by activation of CRF receptors [34].

Hippocampal damage by excessive glucocorticoids

Sustained high levels of glucocorticoids cause damage to the hippocampus [34,35,36,37,15], which can manifest itself as impairment in verbal memory [34,37] and learning [38], as well as hippocampal atrophy [37]. The damage to the hippocampus can include neuron death caused by glucocorticoid-mediated excitotoxicity [38]. The impairment of verbal memory by excessive glucocorticoids may contribute to the language deficits seen in the autistic spectrum. In Kindergarten and early grade school, general memorization difficulties might be seen as a learning disability, since on these levels, education mainly relies on memorization. By itself, the long-term hippocampal damage resulting from excessive levels of glucocorticoids impairs social function, and thereby contributes to the stress experienced in social encounters, and subsequently to the degradation of social function. Hence, there exists yet another vicious circle, this one spanning a time that is long enough for the hippocampal damage to develop. This vicious circle will be referred to as the "very long loop".

Selective delay of language development

Aspects of SI selectively impact language development. The cognitive processing of sensory input from the social interaction by the prefrontal cortex is affected by the stress generated by the social performance expectation, and by the memories of past performances. Expected performance is predominantly of the verbal type requiring language skills. Thus, there is a strong language-type component to the emotional tag which is added to the processed sensory data in the prefrontal cortex. This component may be further enhanced by the BLA. The social function is multidimensional, and so is its stress-driven impairment. In view of the dynamics discussed, one expects the language component of the impairment to be selectively enhanced.

Can frequent severe SI-SD episodes drive children toward autism?

In the developing child, stress instability, severe enough to cause shutdowns**,** can also cause pathological changes in the CNS as well development delays, both of which are intensified through the dynamics of the long loop and the very long loop. The symptoms that can result from SI-SD episodes include delayed language development, learning disability, social avoidance, gaze avoidance, as well as rhythmic motor activity and sensory stimulation and self-injurious behavior.

The first two of these symptoms are expected from the SI-SD dynamics and resulting damage mechanisms discussed above. The social avoidance and gaze avoidance result from attempts to limit social stress, either of situational nature or as a learned behavior.

The symptoms of rhythmic activity or stimulation are understood as learned behavior in response to chronic severe stress. The response relates to the fact that at certain low frequencies rhythmic sensory stimulation has a calming effect, as is well known to mothers who rock their babies, and to people who relax in a rocking chair or hammock. Rhythmic motor activity results in periodic sensory input through muscle spindles and stress receptors, and also through cutaneous thermal receptors that respond to cooling by weak air currents relative to the body that arise as a consequence of the motion. The most effective frequencies appear to be close to the rhythm of a relaxed walk. We think that a sensory resonance mechanism develops prenatally in response to rhythmic stimulation of the vestibular nerve during relaxed walks of the mother, paired with certain circulating hormones. Children who rock or go through other rhythmic movements simply try to calm themselves. It has been found that autistic children tend to engage in more rhythmic motor activity when difficult academic tasks are introduced [32]. A link between rhythmic stimulation and release of BE has been hypothesized [39].

The last symptom mentioned, viz., self-injurious behavior, is understood as behavior of chronically stressed

children, aimed at calming themselves through extra release of BE. Apparently, such children find the pain of self-inflicted injury worth the sedation brought on by the BE released in response to the injury.

Young children may already have CNS impairments or development delays within the autistic spectrum at the time when SI first comes into play in their lives. In such cases it is difficult or impossible to trace the origin of symptoms as they develop or become apparent. However, the damage mechanisms due to SI-SD are just as active in the cases with pre-existing autistic conditions, so that it is important to limit or avoid SI-SD episodes in any case.

How does SI get started in the first place?

If the components of the stress processing system have a graded response for small perturbations, and their reactivity and sensitivity results in a positive instability growth rate, then an initial perturbation of any magnitude will set off the instability. Such “soft excitation” type instability is illustrated by a lead pencil standing on its point. Contrast this with an instability that requires “hard excitation” to manifest, such as a pendulum clock.

The stress instability as defined appears to require only soft excitation. This means that *any* social defect or development delay can set off the SI. Thus, the crucial parameter here is not the initial level of impairment, but the instability growth rate. The instability growth rate is determined by the sensitivity to social stress and the reactivity of the stress-processing neural substrates. In young children, these parameters initially depend on genetic and environmental factors such as prenatal exposure to hormones and other substances circulating in the mother’s blood.

Does SD define a subtype in the autistic spectrum?

Our explorations indicate that SD may be quite common among autistics. Accounts of SD by autistic adults are shown in APPENDIX II. In attempting to assess the incidence of SD in the autistic spectrum the question arises whether an observed SD-like state is real-that is, driven by physiology and therefore involuntary, or feigned. The question can usually be settled by appropriate use of rewards and clinical methods. If avoidance behavior is clearly indicated, the state should not be considered SD as defined above. On the other hand, it may be that many autistic children suffer shutdowns that are unrecognized by parents who have not looked for these patterns in their children, and by physicians who have not inquired about them.

INTERVENTION

Early Detection

Shyness is an early sign of hypersensitivity to social stress which was apparent in the SD child as an infant. Since prosocial behavior develops rapidly in the second year of life, this is the time when intervention may be the most effective [40]. Shyness should be among the earliest criteria for identifying a child at risk for autism because it appears very early and it is easily recognized by parents. Appropriate referrals for more specific screening, assessment and diagnostic services can then be made with little risk of misdiagnosing or missing early symptoms. The benefit of recognizing developmental problems early far outweighs the inconvenience of a screening procedure.

Identifying and controlling triggers

In order to eliminate SD, the triggers must first be identified and then controlled. Social context, tasks, health, and environmental factors should be considered. It is equally important to identify when stress reactions *do not* occur. Children may exhibit stress reactions differently and shutdowns may go unrecognized, especially if others assume the child is engaging in intentional avoidance behavior.

Once the triggers are recognized, they must be managed in order to reduce the child's stress reaction. Parents seeking to help their children may inadvertently make matters worse by insisting on over-scheduling the child in activities and therapies. This may require reducing the child's schedule and thus a philosophical shift away from a "more is better" approach to intervention.

Parents should observe their child closely and collaborate with teachers and therapists to identify the circumstances under which the child shows stress, what the symptoms are, and what seems to help the child recover. A detailed discussion about recognizing and managing triggers appears in the parent version of this paper.

Managing and minimizing triggers to the stress reaction both at home and at school has resulted in significant improvement in the SD child. Over a period of 6 months she has overcome most of her fears, returned to a more normal sleep pattern, became more socially engaged and performed better in academics.

Management in school

The National Autistic Society of the UK has developed an enlightened intervention approach for working with autistics, designated by the acronym "SPELL" (Structure, Positive approaches and expectations, Empathy, Low arousal, Links)**.** The role of "Low Arousal" as a cornerstone of the program is unique among the interventions reviewed [41].

No matter which intervention approach is used, parents need to know whether their child is prone to SD in order to advocate appropriate service for their child in school. A description of the symptoms and triggers of shutdowns, as well as the importance of avoiding them should be written into the IEP document The goal of the parents and educators should be first and foremost to minimize the social stress on the child and avoid shutdowns, *even at the expense of completing schoolwork*. This will put the child at ease and make her receptive to learning. In our view, this is the only way to instill in the child an acceptance of school work and hopefully, a desire to learn. Ultimately the child should learn self-management, a "pivotal" skill which can produce improvements in wide areas of functioning [42].

Close monitoring, rest breaks, and social distancing techniques should be incorporated into the child's school day. A detailed discussion of these techniques appears in the parent's version of this paper [54].

Pharmacology

In view of the issue of side effects, our comments in this section are mere suggestions, and should not be seen as recommendations.

Since the stress of frequent severe SI-SD episodes causes CNS damage and development impairment, it is important to reduce the stress or avoid these episodes altogether. This is best achieved through psychological and management methods. If pharmacological intervention is needed as a last resort, it would be preferable to aim specifically at controlling SI-SD rather than at limiting general anxiety. Similarly, SI-SD would be best controlled by intervening in the early dynamic aspects of the instability, i.e., the instability growth rate, physiological limiting that curbs the run up, and the perseveration, in that order. The instability growth rate can be diminished by decreasing the social function sensitivity and the BLA hyperreactivity. Since the mechanism for stress-driven social function impairment is currently unknown, we have no suggestion as to how the social function sensitivity can be diminished. The hyperreactivity of the BLA, and therefore the instability growth rate, can be decreased through a CRFR1 antagonist such as R121919 [15]. The instability run up can be curbed through a CRFR2 agonist. We are not aware of such an agonist at this time, but CRFR2 has been suggested as a potential target for therapeutic modulation of angiogenesis [43].

In pharmacological stress management of a more general type, it is preferable to engage second messenger mechanisms rather than ligand-mediated direct ion gate control. The second messenger mechanism is activated through G-protein-coupled receptors which are sensitive to small concentrations of ambient neurotransmitters [44]; once the mechanism is activated, the resulting membrane leakage current, which shifts the neuron spiking frequency, lingers for a considerable time [44]. Along these lines, the opioid receptor OP4, also known as ORL1 or LC132, offers interesting opportunities. The receptor differs considerably from the classical opioid receptors OP1, OP2, and OP3, previously called delta, kappa, and mu. The rather recently discovered neuropeptide nociceptin [45], also known as OFQ/N, binds with high affinity to OP4, but not appreciably to OP1, OP2, and OP3. Nociceptin modulates stress, as was shown clearly by experiments with mice that lacked the nociceptin gene [46]. These mice showed elevated levels of plasma corticosterone and impaired adaptation to repeated stress [46]. Furthermore, in rats nociceptin exerts a tonic inhibition of noradrenaline in the BLA [47].

In the human CNS, nociceptin is distributed much like in the rat [48]. What is important in the present context is the extrapolation that children lacking the nociceptin gene are expected to have elevated stress levels and impaired adaptation to repeated stress, and therefore may be subject to SI-SD episodes. At present, testing autistic children for the gene does not appear practical. An OP4 agonist has recently been synthesized in the form of Hoffman-LaRoche Ro 64-6198 [49]. It readily penetrates the brain and has high affinity for human OP4, with a 100-fold selectivity over OP1, OP2, and OP3 [50]. Ro 64-6198 has a low bioavailability (about 4%), but parenteral injection is reported to result in excellent brain penetration [51]. In rats, Ro 64-6198 has been seen to elicit dose-dependent anxiolytic-like effects [50]. Ro 64-6198 appears to be available for experimentation but not for clinical use. In addition to the nonpeptide Ro 64-6198, there is a peptide OP1 agonist [Arg14,Lys15]NC [51].

CONCLUDING REMARKS

In this paper a path is outlined that leads from social function impairment by performance expectation-mediated stress to symptoms in the autistic spectrum. The path, which at present is partly conceptual and partly physiological, passes through the shutdown state. The begin and end point of the path represent a physiological reality, as does the intermediate point that represents SD. Some of the details of the path leading from the initial point to SD are ill defined, vague, or speculative. However, existence of a connection between the initial point and SD can hardly be denied, considering our observations of the SD child, together with the notion of instability that is well known in system analysis. Although the first part of the path, leading up to SD, may be questionable in some of the details, it is supported by the effectiveness of our intervention in the SD child. The second part of the path, that leading from SD to symptoms in the autistic spectrum, is solidly supported by contemporary physiology.

APPENDIX I

Mathematical model for calculating the time course of CRF concentration

The free CRF concentration that results from a uniform CRF release that is maintained for a period of t_1 minutes can be calculated approximately with the following simple mathematical model. Let $n(t)$ be the free CRF concentration at time t, measured in minutes, and let CRF be released at a constant rate s. During the CRF release one has

$$dn/dt = s - an , \qquad (1)$$

where a is the CRF disappearance rate that would occur for zero s. The constant a is expressed in terms of the source-free disappearance half time T as

$$a = 0.693/T , \qquad (2)$$

the numerical factor being the natural logarithm of 2. For an initial CRF concentration of zero, the solution for the differential equation (1) is

$$n = (s/a)(1 - \exp(-at)), \quad 0 < t <= t_1 , \qquad (3)$$

where exp(.) is the exponential function.. After the CRF release has stopped at $t = t_1$, one again has Eq. (1), but now with s=0, and with the solution

$$n = n(t_1)\exp(-a(t - t_1)), \quad t > t_1 , \qquad (4)$$

where $n(t_1)$ is the value for n obtained from Eq. (3) for $t = t_1$.The function $n(t)$ given by Eqs. (3) and (4) has been calculated and plotted in Fig. 2 for the cases specified.

APPENDIX II

Shutdowns in autistic adults

In April 2004, we posted a message on an internet message board (Google group: alt.support.autism) for autistic adults. The posting generally described shutdowns in the SD child.

A dozen or so responders generated over 50 messages discussing the syndrome. They recognized it and indicated that shutdowns are well known among autistics, but not taken seriously by either the medical community or by their coworkers. One said, "trying to fight off shutdown is among the most stressful things I have had to deal with."
Summarized descriptions include:

1 A flood of conflicting signals which makes deciding on one priority impossible.
2 Feeling suddenly very sleepy.
3 The ability to hear, move, make decisions, respond, evaluate information is shut-off.
4 Feeling confused, noisy.
5 Unawareness of the passing of time.
6 A sense of paralysis or heaviness.
7 Like a panic attack.
8 Getting tingly all over and nauseous.
9 Breathing heavily.
10 My tongue turns into a big dry sponge.
11 My sense of smell sharpens.
12 My Ears ring, eyes blur in and out.
13 I can't move because I might attract attention, which is the last thing I want.
14 Everything gets too bright and loud, running at a speed faster than normal.
15 Like having 4 drill sergeants screaming conflicting orders at you at once and if you don't do everything right away you will be in big trouble and you don't know what to do first so you stand there being yelled at.

When asked what makes a shutdown worse?
"When people tell me to "buck up"," get over it" or say, "there is nothing wrong with you".
"When people do not understand and continue to try to engage me, I may snap, get angry or start crying for no reason. I will usually be able to get over it in an hour or so if people just leave me alone."

What makes it better?
Respondents indicated time, sleep, rhythmic rocking, spinning, "stimming", working puzzles, and spending quiet time alone.

"The recovery time depends on the severity of the shutdown and whether the cause is continuing. It can last a few minutes to half and hour, with several hours of after effects".

Autistic writer Donna Williams recalls that as a child she was afraid of "the big black nothingness coming to eat me". As an adult she recognized the syndrome as "sensory flooding triggering such a degree of information overload as to cause an epilepsy-like total shut down on the processing of incoming information" [52].

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