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Intuition and autism: a possible role for Von Economo neurons

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Von Economo neurons (VENs) are a recently evolved cell type which may be involved in the fast intuitive assessment of complex situations. As such, they could be part of the circuitry supporting human social networks. We propose that the VENs relay an output of fronto-insular and anterior cingulate cortex to the parts of frontal and temporal cortex associated with theory-of-mind, where fast intuitions are melded with slower, deliberative judgments. The VENs emerge mainly after birth and increase in number until age 4 yrs. We propose that in autism spectrum disorders the VENs fail to develop normally, and that this failure might be partially responsible for the associated social disabilities that result from faulty intuition.

Intuition and deliberation

When we interact with another person we create a mental model of how that persons thinks and feels. We are likely to have initial, quick intuitions about the person, which are then followed by slower, more reasoned judgments. The mental model is a synthesis of our quick intuitions and our slower deliberations. Intuition uses probabilistic logic whereas deliberation uses inductive and deductive reasoning. Both intuition and deliberation are influenced by emotional value judgments. Describing subjects with Asperger's syndrome, Klin and Volkmar [1] observed, 'their deficient intuition and lack of spontaneous adaptation are accompanied by marked reliance on formalistic rules of behavior and rigid social conventions' ([1], p. 102). In this article, we propose that a subset of cortical neurons known as Von Economo neurons have a possible role in intuition. Our hypotheses are (i) that the Von Economo neurons are an important part of the circuitry responsible for intuition, and (ii) that these neurons are dysfunctional in autism spectrum disorders, resulting in defective intuition.

VEN location and phylogeny

The Von Economo neurons (VENs) are large, bipolar cells located in layer 5 of anterior cingulate (ACC) and fronto-insular (FI) cortex (see Figure 1a–d). They are distinguished from pyramidal cells because they have only a single large basal dendrite whereas pyramidal cells have an array of smaller basal dendrites extending from the cell body (Figure 1e). They were carefully described and mapped in humans by Von Economo and Koskinas [2]. Elsewhere we have referred to them as the 'spindle' neurons, but because of potential confusion with other uses of this term, we now refer to them by the first author of the best description of these cells. They are found only in humans and great apes [3] and are far more abundant in humans than in apes (see Figure 2). They are thus a phylogenetic specialization that has arisen within the last 15 million years in hominoids and have proliferated greatly within the human line of descent. Because of this late emergence in phylogeny, natural selection has had only a relatively short time to shape VEN functioning and integration with other cell populations. Consequently the VENs might be particularly vulnerable to dysfunction in a manner analogous to the propensity of humans to suffer lower back, hip and knee disorders as a consequence of the recent evolution of bipedal posture.

VEN ontogeny

The VENs develop late in ontogeny as well as phylogeny. They first appear in very small numbers in the 35th week of gestation and at birth only about 15% of the postnatal number are present (Figure 2). The adult number is attained by 4 years of age. This postnatal increment in VEN population could arise by differentiation from some pre-existing cell type, or by migration from a potentially proliferative zone in the ventricles [4]. Whether the VENs emerge by differentiation or migration, there is the possibility that their emergence might be disrupted during postnatal development with dysfunctional consequences related to neuropsychiatric disorders. In all of the great ape and postnatal human brains the VENs are ~30% more numerous in FI in the right hemisphere than in the left. However they are only ~6% more numerous in the right hemisphere in the neonates. These data indicate that the strong and consistent predominance for the right hemisphere emerges postnatally. This right hemisphere VEN predominance may be related to the right hemispheric specialization for the social emotions [5,6]. The fact that this 30% right preference is so tightly regulated and consistent across postnatal humans and apes suggests that it is important for normal functioning and that deviations from this ratio could be dysfunctional. In MRI-based comparisons of the left and right hemispheres in a large population of normal subjects, the cortical gray matter volume was greater in the right FI, which is consistent with the rightward predominance of the VENs in this area [7].

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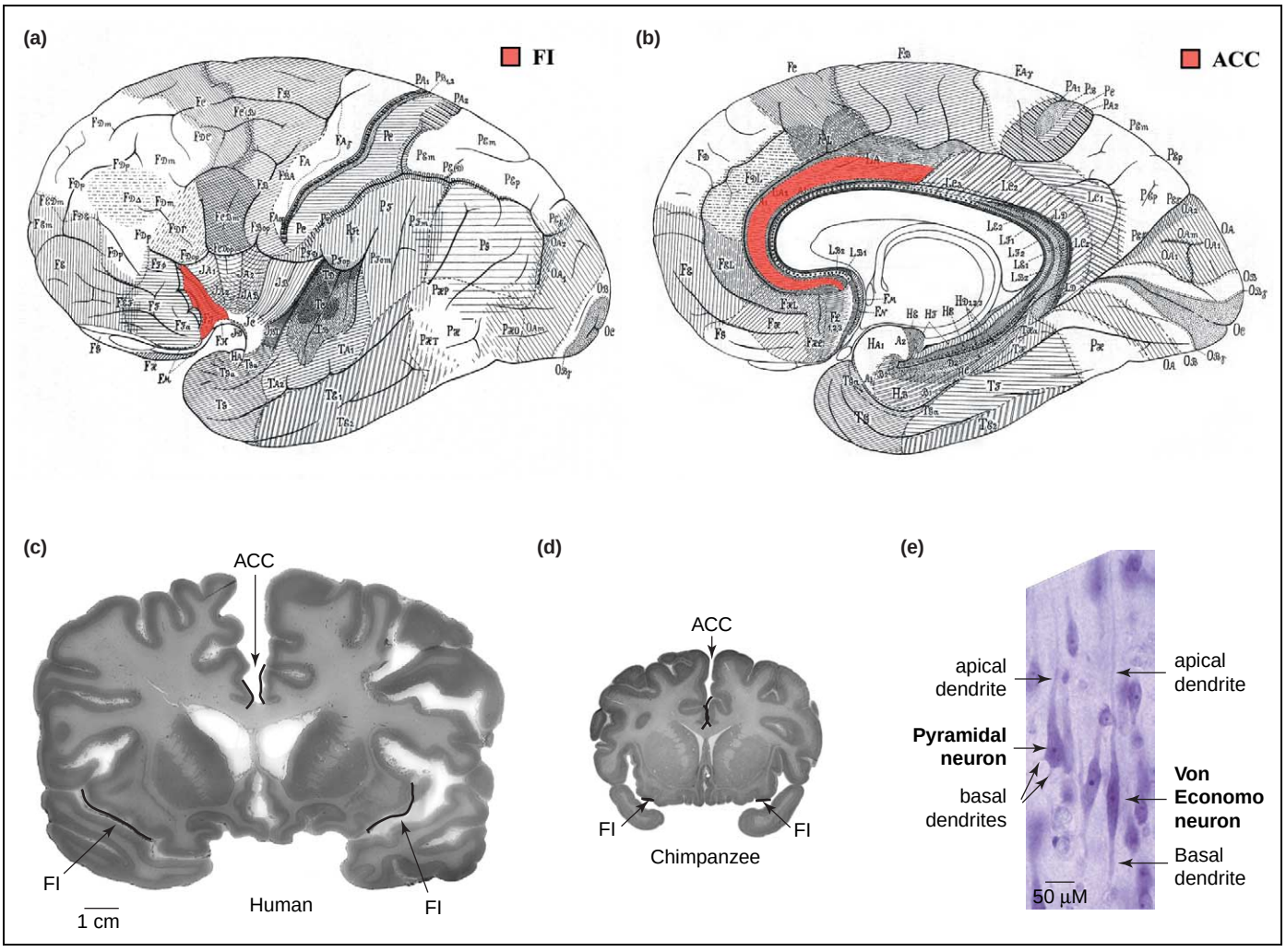

Figure 1. Regions of the brain containing Von Economo neurons (VENs). **(a)** A lateral view of the brain, with fronto-insular cortex (FI) shown in red. **(b)** A medial view of the brain, with anterior cingulate cortex (ACC) shown in red. Adapted from Von Economo and Koskinas [2]. **(c)** FI and the spindle-cell-containing region of ACC indicated on coronal sections through a human brain (50-year-old female) and **(d)** a common chimpanzee brain (sections shown with the right hemisphere of the brain on the right of the figure). Sections are from the Yakovlev Brain Collection at the National Museum of Health and Medicine, and were scanned by the authors. Note that FI is much larger in the human than in the chimpanzee. **(e)** A Von Economo neuron and a pyramidal neuron in layer 5 of FI. Both types of neuron have a single apical dendrite, but note that the VEN also has only a single basal dendrite, in contrast to the pyramidal neuron's multiple basal dendrites. Photomicrograph by the authors of a section from the 50-year-old human brain shown in part (c).

VEN morphology and connections

The dendritic architecture of neurons reflects the way in which they integrate information. The apical dendrites of VENs are very similar to those of the apical dendrites of neighboring pyramidal cells. However, the basal dendritic pattern of the VENs is simpler than that of the pyramids (Figure 1e). In ACC, the average VEN is 4.6 times larger than the average layer 5 pyramidal cell [8]. Their large size suggests that they bear large, rapidly conducting axons, which is a characteristic feature of big neurons in layer 5 elsewhere in the cortex [8,9]. Thus the function of the VENs may be to provide a rapid relay to other parts of the brain of a simple signal derived from information processed within FI and ACC. Lipophilic dye injected into the anterior part of the cingulum bundle backfills VENs in ACC, thus indicating that they are projection neurons [10]. However, it is not known where the VENs ultimately project. Studies in monkeys indicate that ACC and FI connect to prefrontal, orbitofrontal, insular and anterior temporal cortices, the amygdala, hypothalamus, various thalamic nuclei, and the periaqueductal gray [11–13].

VEN neurotransmitter receptors: social bonding, reward and punishment

VEN functions are revealed by immuno-cytochemical staining with antibodies to neurotransmitter receptors. The neurotransmitter receptors expressed on the VENs suggest that they are involved in the formation of social bonds, and the anticipation of reward and punishment in uncertain conditions. The VENs form part of a limited set of layer 5 neurons that are stained with the vasopressin 1a receptor in FI and ACC (see Figure 3a). The vasopressin 1a receptor in the ventral pallidum of the forebrain is strongly linked to the formation of social bonds in rodents [14]. ACC and FI are activated when subjects view an image of a loved one compared with that of an acquaintance, suggesting that there might be an involvement of these structures in bonding [15]. In hominoids the system

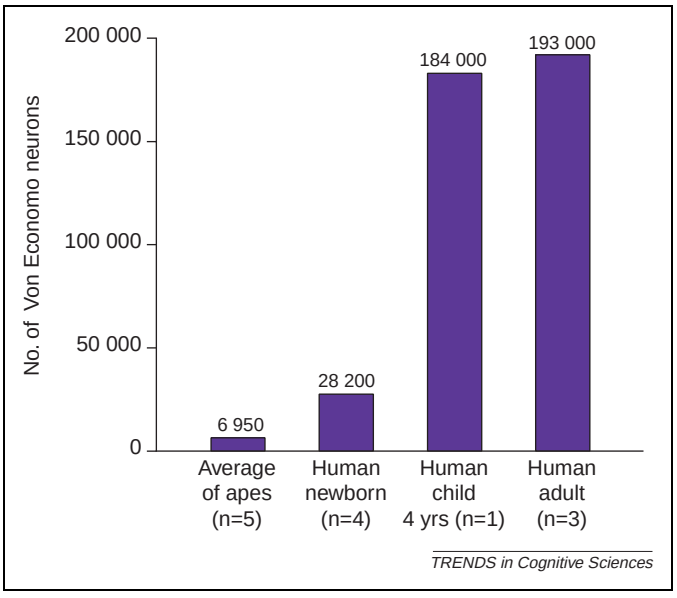

Figure 2. Comparison of Von Economo neuron numbers. Total number of VENs in FI (total of right and left hemispheres) is shown for apes, human neonates, a four-year-old child, and an adult human. The number of subjects is given in parentheses. The data are stereological counts by the authors on brains in the Yakovlev Collection at the National Museum of Health and Science and the Semendeferi Collection at the University of California, San Diego.

for social bonding is likely to be greatly elaborated and heavily influenced by more plastic cortical circuits of which the VENs are a component.

Dopamine D3 receptor

The VEN are strongly labeled with antibodies to the dopamine D3 receptor (Figure 3b), which is a high affinity dopamine receptor that has been proposed to signal the expectation of reward under uncertainty [16]. When reward is uncertain, the source of the cortical input, dopaminergic neurons in the ventral tegmental area, exhibit a steady ramp-like increase in activity associated with excited expectancy culminating in the receipt or non-receipt of the reward (see Figure 4). This expectancy-related activity increases as a function of uncertainty, and it may be monitored by the high affinity dopamine receptors. The high affinity dopamine receptors in the VENs may signal the expectation of reward under uncertain conditions. The activation of FI and ACC increases with the degree of uncertainty (Figure 4) [17]. FI and ACC activity is coupled to situations in which the subject sustains a gambling loss (punishment) and then switches to a different behavioral strategy, implying that in normal subjects these areas are involved in adaptive decision-making and cognitive flexibility [18]. FI is also activated in gambling tasks when the subjects anticipate that their luck is about to change, which is a form of intuition [19].

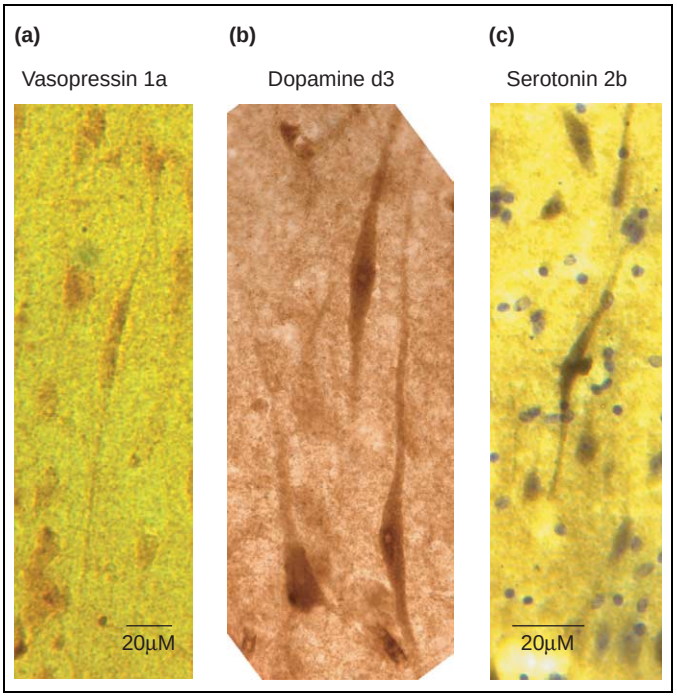

Figure 3. Immunocytochemistry of Von Economo neurons. VENs in ACC of male humans, labeled with antibodies to: **(a)** the vasopressin 1a receptor, which has been linked to the formation of social bonds in rodents [14]; **(b)** the dopamine d3 receptor, a high-affinity receptor potentially linked to the anticipation of reward under conditions of uncertainty; and **(c)** the serotonin 2b receptor (counterstained with cresyl violet), which may be linked to the anticipation of punishment. (a) and (b) are from ACC in a 53-year-old male; (c) is from ACC in a 54-year-old male.

Serotonin 2b receptor

The serotonin 2b receptor is strongly expressed on the VENs (Figure 4c) and is rarely expressed elsewhere in the central nervous system [20]. However, the serotonin 2b receptor is also strongly expressed in the human stomach and intestines where it promotes contractions of the smooth muscles responsible for peristalsis [21]. Serotonin might serve as an antagonistic signal to dopamine, with serotonin signaling punishment and dopamine signaling reward [22]. The activation of the serotonin 2b receptor on VENs might be related to the capacity of the activity in the stomach and intestines to signal impending danger or punishment (literally 'gut feelings') and thus might be an opponent to the dopamine D3 signal of reward expectation. The outcome of these opponent processes could be an evaluation by VEN of the relative likelihood of punishment versus reward and contribute to 'gut level' or intuitive decision-making in a given behavioral context. ACC and FI are known to have an important role in interoception or the conscious awareness of visceral activity [23].

In his theory of 'somatic states', Damasio [24] proposed that such monitoring of sensations arising from the gut is crucial to adaptive decision-making. The presence of a serotonin receptor on the VEN that is otherwise rare in the brain, but common in the viscera, suggests an interesting extension of the concept that these areas are monitoring activity in the gut. Perhaps, the expression of the serotonin 2b receptor on the VEN represents a transposition of this function from the gut into the brain, which would enable the organism to react more quickly to threatening circumstances than if it depended solely on monitoring sensations arising from the gut.

VENs and intuition

Intuition is a form of cognition in which many variables are rapidly evaluated to yield a fast decision. Typically we are unaware of the logical steps or assumptions underlying the process although intuition is based on

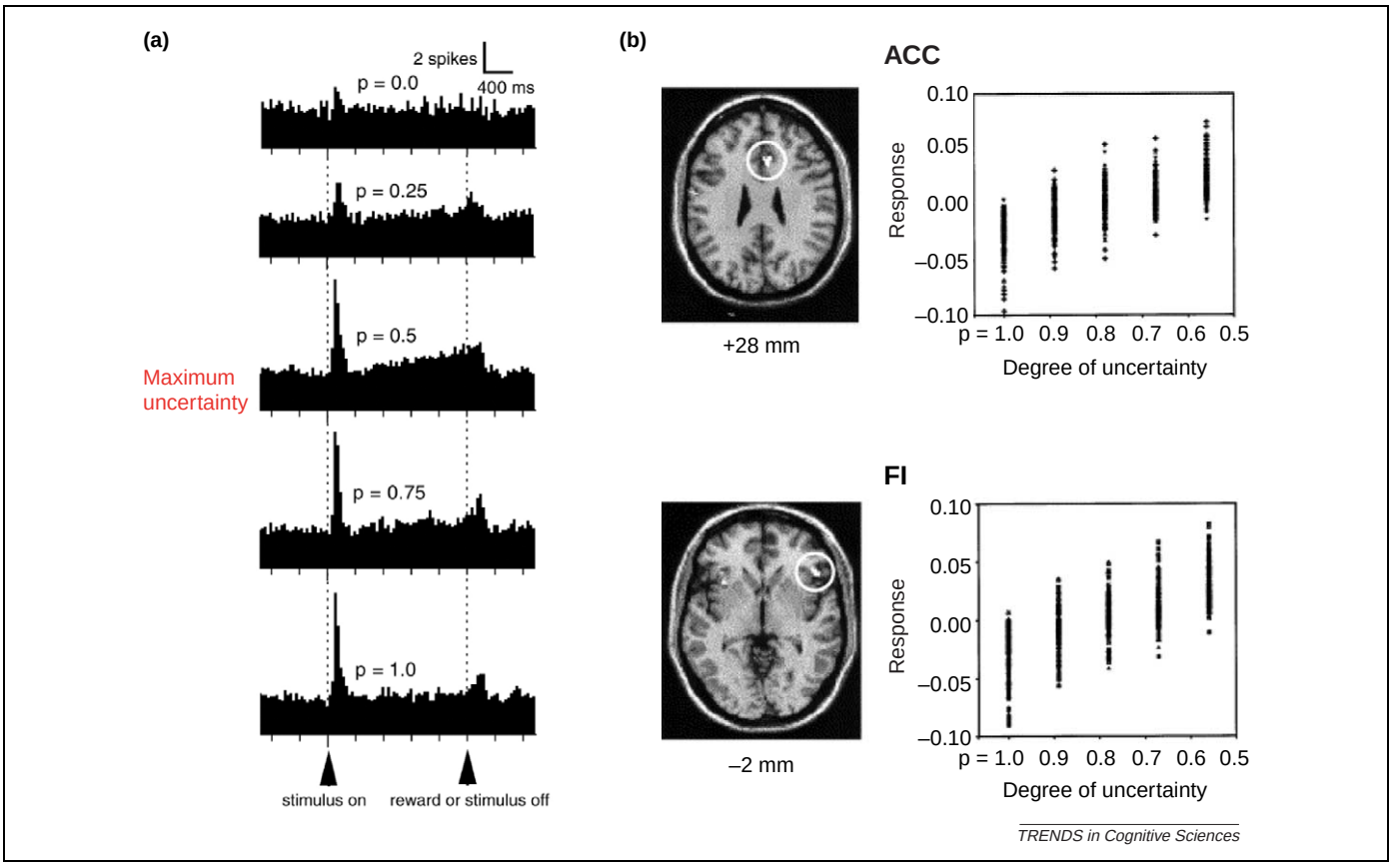

Figure 4. The effects of uncertainty. **(a)** Histograms of single-unit recordings of dopaminergic neurons in the ventral tegmentum of the macaque monkey show a ramp-like build-up in activity during the anticipation of uncertain rewards [51]. Two monkeys were conditioned with distinct visual stimuli indicating the probability (P=0.0, 0.25, 0.5, 0.75, and 1.0) of a liquid reward being delivered. After the initial peak at the time of stimulus onset, the sustained activation was greatest in the P=0.5 condition, in which there was maximum uncertainty about whether a reward would be forthcoming. Reprinted with permission from [51]. Copyright 2003 AAAS. **(b)** Modulation of anticipatory-delay-period activity by risk. Activity during delay was modulated by decision uncertainty in the areas of anterior cingulate cortex (ACC, top) and fronto-insular cortex (FI, bottom). Note the (circled) activation in the right hemisphere. Subjects were presented with a numerical playing card (cue card) with a value from 1 to 10, and then asked to guess whether the next card would be higher or lower. After a delay, the next card was revealed and a monetary reward or penalty assessed. During the delay, the level of uncertainty as to the outcome varied depending on the value of the cue card. The plots adjacent to each section show how activity in that region was modulated by the degree of uncertainty. Adapted with permission from [17].

experience-based probabilistic models. We experience the intuitive process at a visceral level. Intuitive decision-making enables us to react quickly in situations that involve a high degree of uncertainty which commonly involve social interactions. Frequently we do not have the luxury of sufficient time to perform deliberative cost-benefit analyses to determine the most appropriate course of action, but instead must rely on rapid intuitive judgments. ACC and FI are active when subjects make decisions under a high degree of uncertainty [17]. These areas are involved in the subjective experience of pain [25], which is powerfully magnified by uncertainty. These areas are also active when subjects experience guilt, embarrassment and engage in deception [26–28]. ACC and FI are also active in humor (Watson and Allman, unpublished fMRI data), trust, empathy, and the discrimination of the mental states of others [25,29,30]. All of these social emotions are influenced by the degree of uncertainty involved. As of yet, we do not know the mechanisms responsible for the differentiation of the complex social emotions that activate FI and ACC, but we do know that the VENs are a recently evolved population that probably serves to relay output of the processing within FI and ACC to other brain structures. Their large size suggests that the VENs may relay a fast intuitive assessment of complex social situations to allow the rapid adjustment of behavior in quickly changing social situations. They can thus be seen as an adaptation supporting the increased complexity of hominoid and especially human social networks. This is refected in evidence that the capacity for empathy is better developed in chimpanzees than in monkeys [31]. We hypothesize that the VENs and associated circuitry enable us to reduce complex social and cultural dimensions of decision-making into a single dimension that facilitates the rapid execution of decisions. Other animals are not encumbered by such elaborate social and cultural contingencies to their decision-making and thus do not require such a system for rapid intuitive choice.

Possible links to neuropyschiatric disorders

We hypothesize that the VENs are particularly vulnerable to dysfunction owing to their late emergence in phylogeny and ontogeny, and that such dysfunctions may be part of the pathogenesis of several neuropsychiatric conditions known to involve FI and ACC, such as obsessive-compulsive disorder [32], psychopathy [33] and fronto-temporal dementia (Seeley and Allman, unpublished data).

We hypothesize that the social disabilities in autism spectrum disorders are partially due to abnormal development of the VENs. We believe that these disabilities may cause poor intuitive decision-making in situations involving considerable uncertainty, especially in social contexts. More broadly, our hypothesis is that the VENs and related structures integrate the probability of reward and punishment derived from many inputs and enable individuals to make quick, intuitive decisions that enable them to adapt to rapidly changing conditions. Because social emotions by their very nature involve considerable uncertainty, and because social interactions are often of a rapidly changing nature, an impairment of the VEN system would be predicted to compromise social functioning. The lack of quick social intuitions is a key deficit in autism spectrum disorders. For example, Klin and Volkmar have observed:

> Individuals with Asperger's syndrome typically cannot avail themselves of their formal social knowledge in quick-paced, simultaneously shifting, social situations. They often miss the tempo of the interaction and lose any possibility of rapidly adjusting themselves to the forever shifting social and communicative demands of others. ([1], p. 110).

This is exemplified by the compensatory strategy formulated by a high functioning autistic individual who reported:

> When I encounter a new social situation, I have to search my memory for a similar experience that I can use as a model for my next action…I have a very difficult time when I am confronted with unexpected social surprises. For common social interactions with clients I use preprogrammed, prerehearsed responses. Everything is done with logic. ([34], p. 1039).

However, difficulties dealing with non-social uncertainty may also be present. For example, Kanner observed of autistic children:

> The child's behavior is governed by an anxiously obsessive desire for the maintenance of sameness. Changes in routine…can drive him to despair. ([35], p. 245).

In short, we believe that the VEN system for rapid, intuitive responses in situations involving considerable uncertainty is impaired in autism spectrum disorders. We are not proposing that the VEN system is responsible for theory of mind, but rather may serve as a input to the system which creates mental models of the thinking of others. This system includes the paracingulate cortex, just superior to the part of ACC that contains VENs [36]. The lack of intuition could force autistic subjects to rely on slower deliberation.

The possibility that dysfunctions of the VENs might be linked to autism has been raised twice before. Frith suggested that defects in theory of mind in autism might arise from weak connections between medial frontal and anterior temporal lobe structures [37], and in this context mentioned the VENs in ACC as projecting neurons that might be defective in this disorder. Our view is consistent with this theory in its emphasis on potential disruption of connections in autism, but we believe that the main role of the VENs is in intuition. Mundy [38] noted the postnatal emergence of the VENs [39] and suggested that the VENs might be involved in experience-expectant processes, as well as experience-dependent processes, that are disrupted in autism. This interpretation in consistent with our hypothesis concerning the role of the VENs in the integration of the expectations of reward and punishment.

Evidence linking autism with ACC and FI

A structural MRI study of 17 individuals with autism spectrum disorders found that the portion of the ACC in the right hemisphere that contains the VENs was reduced in volume relative to matched controls [40]. In a diffusion tensor imaging (DTI) study, the long distance fiber connections located in the white matter adjacent to ACC were disordered in autistic relative to normal subjects [41]. This disordered white matter includes the anterior part of the cingulum bundle, which in normal subjects carries the axons of VENs [10]. In a postmortem analysis of autistic individuals, Kemper and Bauman found that the ACC was poorly laminated [42]. There are also isolated pockets of neurons in the white matter of frontal cortex, suggesting neuronal migration defects in autism [43,44]. There is also evidence for abnormalities in the pattern of postnatal growth of the frontal lobes in autism during the first few years of life, the period of emergence of the VENs [45]. In our preliminary studies of the autopsy brains of an autistic 9 year old boy and a 9-year-old girl, we have observed heavy concentrations of VENs located in the white matter and extending through layer 6 into layer 5 in FI (Allman *et al.*, unpublished data). The VENs in these autistic subjects were also located medially to their normal location in FI. These findings suggest that the cellular architecture and connections of ACC and FI may be disordered in autism as part of a more extensive pattern of abnormal growth in this disorder [43–46].

There is also direct functional imaging evidence linking FI with autism. High functioning autistic subjects and controls were asked to discriminate the mental states of individuals depicted in photographs. The region corresponding to FI on the right side was activated in normal subjects but not in the autistic subjects [30]. In normal subjects, feelings of empathy [25] and embarrassment [27] activate FI and ACC. Measures of embarrassment and empathy have been reported to be reduced in autistic subjects although there is considerable overlap between autistic and normal subject populations. [47–49]. These results in structured tests contrast with consistent reports of severe social impairments in autistic subjects in normal, unstructured interactions [1,35]. That these impairments are more likely to manifest themselves in unstructured situations is consistent with the theory that there is a basic defect in autism in a system responsible for intuitive judgment under uncertain conditions.

Summary and conclusions

Von Economo cells are a recently evolved population of cortical neurons, which may be involved in the fast

Box 1. Questions for future research

- Are the Von Economo neurons (VENs) abnormally located and connected in autism and other disorders?
- If so, how specific are these defects to the VENs relative to other neuronal populations?
- Is the hemispheric distribution of the VENs abnormal in autism and other neuropsychiatric disorders?
- Are the expression of neurotransmitter receptors and dendritic morphology abnormal in the VENs in autism and other neuropsychiatric disorders?
- Is it possible to obtain non-invasive measures correlated with the VENs through brain imaging?

intuitive assessment of complex situations. These cells emerge mainly after birth and reach their adult number by age 4. We propose that in autism spectrum disorders the VENs fail to develop normally and that this failure could be partially responsible for the social disabilities in these disorders as a result of faulty intuition. Our theory predicts that autistic subjects will be abnormal in making intuitive decisions under conditions involving a high degree of uncertainty. We further predict that these deficiencies will be most clearly manifested in social situations, but will be observable in non-social tasks, such as those involving gambling or ambiguity. For example, these abnormalities might involve delayed responses, poor adaptation to rapidly changing circumstances, or abnormal physiological responses. Our theory also predicts that there will be abnormalities in the location, number and connections of VENs in FI and ACC in autism (see also Box 1). In normal subjects there are consistently ~30% more VENs in the right hemisphere in FI and this ratio develops in the early postnatal period. Abnormal hemisphere distribution might be associated with pathological functioning in various disorders. There might also be abnormalities in the expression of neurotransmitter receptors or dendritic morphology of the VENs, because such abnormalities might be expected disrupt the integration of signals hypothesized to occur in the VENs in relation to reward, punishment and social bonding. As the serotonin 2b receptor is rare in the brain but strongly expressed on the VENs and a specific ligand for this receptor has recently been developed [50], this class of receptor on the VENs and closely related neurons could be monitored in FI and ACC using positron emission tomography. Finally, we suggest that the VENs might also play a role in bipolar and obsessive-compulsive disorder, anorexia, psychopathy and fronto-temporal dementia.

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