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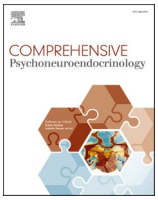

Tales from the life and lab of a female social neuroscientist

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ABSTRACT

This narrative review charts my unconventional path to becoming a social neuroscientist and describes my research findings – some baffling, some serendipitous, some pivotal – in the field of neuropeptide biology. I trace my childhood as a Bell Labs "brat" to my adolescence as a soccer-playing party girl, to my early days as a graduate student, when I first encountered oxytocin and vasopressin. These two molecules instantly captivated – and held – my attention and imagination. For more than 25 years, a core goal of my research program has been to better understand how these neuropeptides regulate social functioning across a range of species (e.g., meadow voles, mice, squirrel monkeys, rhesus monkeys, and humans), and to translate fundamental insights from this work to guide development of novel pharmacotherapies to treat social impairments in clinical populations. I also discuss my experience of being a woman and a mother in STEM, and identify the important people and events which helped shape my career and the scientist I am today.

1. Early adventures with emerging technologies and conflicting identities

Mine was a peculiar and magical childhood, growing up a Bell Labs "brat." My dad had earned a PhD in electrical engineering from the University of Michigan in 1969, and began his career at Bell Telephone Laboratories, then in its halcyon days of innovation [1]. In 1979, when I was seven years old, my dad purchased an Apple II plus home computer. He also brought home a work terminal and taught my brother Drew and me how to telnet into the Bell Labs mainframe. Dad frequently presided over coding lessons (in which Drew and I grudgingly participated), and as a reward for suffering through them, we were allowed to play games on the mainframe. This included "Adventure" (played on a dot matrix printer) and a primitive version of Space Invaders.

We also had home access to Bell Labs' newest innovations, including call waiting and three-way calling. Drew and I spent many entertaining hours surreptitiously connecting "unsuspecting victims" through three-way calls. Because the technology was relatively unknown to the general public, the two parties would inevitably bicker over who had initiated the call, and, when the experiment succeeded, we could eavesdrop on their ensuing conversation. Our favorite targets were feuding neighbors, romantically-inclined classmates, and McDonald's and Burger King, then at the height of their 1980s era marketing wars. We were shameless. (For the record, our dad did not approve of these activities, and vehemently rejected our defense that they were a valuable "use case" for three-way calling.) Later, our dad stashed brick-like cell phones in our cars and introduced us to email, which he had been using for decades. Although I did not become an engineer, I attribute much of my early interest in science to these childhood interactions with emerging technology.

My childhood passion instead was animals, which my mother fueled both at home and in our frequent outdoor adventures. I grew up surrounded by pet birds, dogs, cats, gerbils, and goldfish. We caught tadpoles in local ponds, befriended a backyard grasshopper that we named Eek, brought hermit crabs home for "sleepovers," and adopted a calico cat that had been abandoned at my grandparents' Midwestern poultry farm. I talked to wild animals, mimicked their calls, and endeavored to understand their behavior. I entertained becoming a veterinarian, because I loved caring for and helping all living creatures.

In high school, I was captivated by anatomy and experimental chemistry, and grew passionate about becoming a physician and treating human disease. This interest was kept relatively secret, however. I had an active social life, and being labeled "smart" in my suburban Chicago high school was decidedly uncool. I often felt there were two Karens: one studious, one fun-loving. To fit in with my less academically-inclined peers, I lied about the number of Advanced

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Placement (A.P.) classes I was taking. I also cultivated an outward image as a soccer playing, Cosmopolitan magazine-reading, boy-crazy party girl. I did not fool everyone, however. I have a clear memory of my A.P. US history teacher, Mrs. Linder, pulling me aside after I received the top grade on an exam in her class. In an exasperated tone, she told me that she hoped I would one day choose a profession that used my brain rather than becoming a "mindless princess." Another important influence was Dr. Hollman, my English teacher. She, too, saw promise in me, encouraged me to take school seriously, and nominated me for a national writing award. Both of these teachers, in their own way, were rooting for "Academic Karen." Although at the time I recall being annoyed by their "meddling," I am now grateful for it. Their encouragement unequivocally contributed to me choosing a more fulfilling career path than I may have otherwise. (Thank you, Kathy and Marilyn!)

Growing up, my relatives often said that I was "genetically programmed" to attend the University of Michigan. My parents had been raised in Ann Arbor and both had attended the university, as had assorted uncles, aunts, grandparents, and even great grandparents. Because my dad's job had taken us all over the country, for stints in Colorado, New Jersey, Connecticut, Michigan, and Illinois, it was Ann Arbor, where our extended family lived during my itinerant childhood, that became my heart's home. Additionally, throughout much of my childhood, my family attended Michigania, a University of Michigan Alumni Association family camp (or, a "propagandist cult," as my future husband would come to affectionately call it). Truth be told, there never was another school for me and, fortunately, I had performed well enough in high school to matriculate to the University of Michigan in 1990, where I would remain for 10 glorious years.

2. College: the doctoral fork in the road

My intention was to pursue a premed path, but life had other plans. I had tested out of inorganic chemistry on a college placement test, and poor advice from a college guidance counselor, combined with my 18-year-old hubris, had me taking organic chemistry my first semester, while pledging a sorority, attending Michigan sporting events, and largely carousing. This "overcommitment" was worsened by the fact that I despised the rote memorization of "orgo," which so differed from the exciting experiments I had previously conducted in my high school's A.P. inorganic chemistry class. I was a miserable student, and I was fortunate to pass the class. Mercifully, that semester I was also taking introduction to psychology, which I loved for its every day relevance and emphasis on the mind and discovery. This interest was reinforced by spending time with my aunt, Holly Craig, a professor at the university. Aunt Holly had earned a PhD in speech language pathology, and was then director of Michigan's communicative disorders clinic and a principal investigator (PI) on several NIH-funded human subjects' research grants. I loved seeing the arc of discovery through her eyes: from an idea she conceived and empirically tested, to her reflection on what she had learned. Her enthusiasm was contagious, and a career in academia became an abiding goal.

The silver lining to my freshman year organic chemistry debacle was that I now had room in my schedule to take non-premed courses, and I cherished the opportunity to receive a broader education. This enabled me to explore "Big Why Questions": Why are we here? Why do we do what we do? In search of answers, I took memorable courses in religion, bioethics, poetry, history of the holocaust, "abnormal" psychology, linguistics, and anthropology. When I took an evolutionary biology course from the peerless Richard Alexander [2], I found my first academic love. I did not realize it at the time, but Michigan was then one of the best places in the world to study evolution and behavior. I am deeply indebted to my undergraduate professors Richard Alexander, Bobbi Low, and David Buss for cultivating my developing academic mind. I decided to remain at Michigan to pursue a PhD.

3. Graduate school: finding neuropeptides

In the early to mid-1990s, game theory was a core framework [3] that (mostly male) evolutionary scientists were using in a "zero-sum" manner to study human mating and other behavioral interactions. I found this approach limited, as in our own species, biparental care is essentially obligate, and we form deep, abiding ties that bind. I was also skeptical of the just-so stories spun by many evolutionary academics, and I became increasingly interested in studying something more tractable: the proximate neurobiological mechanisms that had evolved to produce mating and parental care attachment behaviors that increase fitness. As luck would have it, I met and began interacting frequently with three University of Michigan psychiatrists through Michigan's Evolution and Human Behavior program. They included Randy Nesse, co-founder of the field of Darwinian medicine [4], Elizabeth Young, a well-regarded stress neurobiologist, and Israel Liberzon, then a newly minted assistant professor. They were the first to introduce me to oxytocin and vasopressin, the former of which Israel and Elizabeth were then studying in the lab [5–7]. Randy and Elizabeth also invited me to attend what would prove to be a life-changing conference: The New York Academy of Science's 1995 Integrative Neurobiology of Affiliation meeting in Washington, DC [8]. There I was introduced to Sue Carter and Cort Pedersen, luminaries of the oxytocin universe, whose publications I had been ravenously consuming for months. I was starstruck.

Randy, Elizabeth, and Israel had learned about oxytocin and vasopressin's classic physiological roles during medical school. However, the more recent neuroscience findings implicating oxytocin and vasopressin in the regulation of mammalian affiliative behavior and attachment bonds [9–13] had us all contemplating the roles they might play in human relationships, as well as in neuropsychiatric disorders. I once again felt the pull of medical school, which intensified when I took a neuroanatomy course from the incomparable Sarah Winas Newman. But it was also clear that even practicing physicians lacked satisfying answers to the questions I was most interested in, and I figured that my efforts were likely to be better spent seeking them at the bench. This matched the collective advice I received from my mentors, which was to train as a basic neuroscientist, and circle back to human research later in my career.

A growing interest in comparative approaches (fostered by Bobbi Low and Warren Holmes) led me to my PhD advisor, Theresa "Terri" Lee. Terri had completed her dissertation on the biological basis of maternal care in Howard Moltz's lab at the University of Chicago and her postdoctoral studies on circadian rhythmicity in Irv Zucker's lab at the University of California (UC), Berkeley. She was everything anyone could want in a mentor: A clear thinker and writer, an excellent experimentalist, and an absolute mensch. Terri treated her trainees as if they were her children. My own mother, with whom I maintain a close relationship, referred to Terri as my "second mom."

Terri was then conducting two lines of circadian research in rodents, one involving Chilean degus (*Octogon degus*) and one meadow voles (*Microtus pennsylvanicus*). Despite her current research focus on circadian biology, Terri had maintained an interest in the neurobiological regulation of social behavior. We soon came to an arrangement: I could conduct oxytocin and vasopressin research under her supervision, so long as I studied a species she already had in the lab and included a circadian component. Terri also mandated that I get up to speed in the premed curriculum, which I had assiduously avoided after organic chemistry. During the next two years, I dutifully enrolled in or audited nearly ten natural science courses to fulfill my promise to Terri. Once sufficiently motivated by their relevance to my research questions, I excelled in them.

I was disappointed that we did not have socially monogamous prairie voles (*Microtus ochrogaster*) in the lab, because they were then the "poster child" for neuropeptide regulation of social behavior [9,11,12,14–16]. However, I soon became fascinated by the closely related, but non-monogamous, "asocial" meadow vole, and its sensitivity to light. I

was surprised to learn that, when housed in the lab under short, winter photoperiods, meadow voles became highly social, and males spontaneously engaged in appreciable paternal care. Intriguingly, this lab observation was supported by evidence from radiotelemetry studies in the field, indicating ecological relevance [17]. I soon learned that intraspecific variation in mammalian social organization is common [18], and many "non-monogamous" species in fact display facultative social preferences and paternal care under certain environmental conditions (i.e., the ones that maximize reproductive success). While the evolutionary origins of facultative social behaviors associated with alternative social systems were already well studied [19], no research had examined the underlying neural pathways that mediated the expression of social behaviors when they were facultatively, rather than constitutively, initiated. I hypothesized that characteristically non-monogamous meadow voles evolved the ability to express facultative partner preferences and paternal care in response to certain social and environmental cues routinely encountered under free-living conditions. I then sought to determine whether the previously described neurobiology that regulated partner preferences and paternal behavior in a characteristically monogamous species (i.e., prairie voles) was similar to the neurobiology that regulates these behaviors in characteristically non-monogamous meadow voles, when they facultatively exhibit social behaviors associated with monogamy. This plan satisfied both Terri and me: I was fulfilling Terri's circadian mandate by studying circannual rhythmicity, and I was able to study neuropeptide regulation of social behavior within an evolutionary framework.

I soon became proficient at measuring mating, affiliative, and parenting behaviors in voles, and gained expertise in central pharmacological and receptor autoradiographic methods, which I used to investigate the roles that oxytocin and vasopressin play in regulating these behaviors. Behavioral data from my dissertation showed that meadow voles readily develop selective partner preferences and paternal behavior under a variety of ecologically relevant circumstances in the lab [20–23], and do so using the same social cues (e.g., mating, cohabitation) as prairie voles. My neurobiological data substantiated these finding, as the neuropeptides previously implicated in the regulation of partner preference formation and paternal behavior in monogamous prairie voles also regulated these same behaviors in typically non-monogamous meadow voles. Specifically, male meadow voles showed significant changes in their paternal state following central administration of vasopressin, whereas administration of a selective V1A receptor antagonist blocked the onset of paternal care [24]. Male meadow voles that behaved paternally also showed different patterns of central oxytocin and vasopressin receptors in the extended amygdala compared with male meadow voles that did not [25]. In females, oxytocin receptor patterns in the extended amygdala reflected differences in seasonal social behavior and the onset of partner preferences [26]. I concluded my dissertation roughly as follows: The most useful way to conceptualize intraspecific and interspecific differences in social organization is to view social systems and the neurobiology which regulates them not as fixed, invariant products of natural selection, but as flexible, adaptive behavioral and neurobiological responses designed by natural selection to best maximize reproductive success under variable socioecological circumstances [27].

4. Next steps and postdoctoral research: changing systems and species

I loved the idea of remaining at Michigan, but I was told in no uncertain terms by my mentoring team that I was being "kicked out of the nest." I could perhaps return to Michigan later in my career, but it was imperative that I "clock some time" at another university for my postdoctoral training. I began exploring the possibility of a fellowship with Cort Pedersen, a psychiatrist at the University of North Carolina, Chapel Hill. Cort had been the first to inject oxytocin directly into the brain of virgin rats and "turn on" maternal behavior [10,28], a possibility that Peter Klopfer, one of Cort's mentors, had foreseen in 1971 [29]. Cort himself had learned about oxytocin while painting Peter's house to earn money. Cort would have been an outstanding postdoctoral mentor for me, but unfortunately, the feasibility of funding me on an institutional NIH T32 training grant became uncertain after its PI abruptly passed away.

Around the same time, my then-boyfriend had a summer internship in Palo Alto, California. He invited me to visit. Terri readily agreed to my plan of writing my dissertation and associated manuscripts remotely. (I suspect she did so to get me out of the lab; I had so many experiments I still wanted to run!) California soon captivated my heart. I loved how the ocean fog rolled over the Santa Cruz mountains in the late afternoon, and I loved the fauna; scrub jays and California ground squirrels were early favorites. As my time in California drew to a close, I became distraught at the prospect of leaving it.

I decided on a whim to email David Lyons, a Stanford University professor who had given an interesting talk I attended several years prior. As luck would have it, David and his collaborator, Alan Schatzberg, had a funded postdoctoral position to study the role of social separation stress in squirrel monkeys (*Samiri sciureus*) as a model for stress-related mood and anxiety disorders. We arranged a meeting for the next day. David showed me the animal colony and I was fascinated by the squirrel monkeys' rich social behavior repertoire. I was also enthusiastic about the opportunity – finally! – to conduct research that was clinically relevant, and which would be supervised by a translational mentoring team consisting of a biologist (David), and a psychiatrist (Alan). Although the old training adage "switch systems or species, but not both" crossed my mind, I took the plunge and relocated to California, where I joined David and Alan's jointly run psychiatry neuroscience research team.

As it turned out, the biggest adjustment for me was not changing systems or species, but transitioning from a psychology department in a large Midwestern public university to a psychiatry department in a small coastal private medical school. On one of my first days in the lab, I happened to be passing by the office of an eminent professor (name withheld to protect the guilty). He was on the phone, with the door open, arguing with a journal editor. I overheard him shout: "You are lucky I even submitted my manuscript to you; I usually only publish in Science or Nature!" Later that day, I made a quick coffee run. There were five of us in line; three were Nobel Laureates.

My training with David and Alan began by writing a review article on the role of hypothalamic-pituitary-adrenal (HPA) axis dysregulation in major depression [30]. Soon after, I was spending long hours in the animal rooms, observing the squirrel monkeys, in the company of Chris Buckmaster, technician extraordinaire, who would become a life-long friend. Although the prevailing view was that early life stress exposure is invariantly pathogenic, young squirrel monkeys that had been exposed to intermittent early life stressors were actually exhibiting better (rather than worse) stress coping abilities. I sought to study this observation empirically. What if certain forms of mild early life stress exposure, instead of producing stress vulnerability, could "inoculate" a developing organism, thereby producing stress resilience [31]? I secured an individual NIH F32 fellowship to test this hypothesis. As predicted, we found that mild early stress exposure produced diminished anxiety and attenuated neuroendocrine responses to later life stressors [32–35], while also increasing prefrontal-dependent cognitive control of behavior [36–39]. We also showed that stress resilience in primates was induced by early life stress exposure rather than mothering [34], as had been previously found in rats [40]. These findings served to reject a decades-old theory that posited all forms of early inducible stress resilience were maternally mediated, and demonstrated to me the power (and peril) of selecting various animal models to approximate and study human disease [41,42].

My expertise in neuropeptide and stress biology, combined with knowledge I had gleaned from attending Alan's clinical lab meetings, renewed my interest in the idea that oxytocin dysregulation may confer

risk to develop stress-related mood and anxiety disorders in humans, particularly when their onset is precipitated by social isolation or loss of a loved one. I became intrigued by the possibility that oxytocin had antidepressant and anxiolytic properties [43]. Funding from a NARSAD Young Investigator award enabled me to begin exploring this hypothesis: I delivered oxytocin intranasally to squirrel monkeys and showed that it decreased social isolation-induced HPA axis activation [44]. As part of this work, we also needed to quantify oxytocin concentrations in individual animals. I was experienced at performing various assays, but, maddeningly, could not measure oxytocin reliably in squirrel monkey samples. I decided to visit Toni Zeigler's Endocrine Core at the University of Wisconsin, where I ran the enzyme immunoassays with her. I later shipped samples to Janet Amico at the University of Pittsburgh and Rainer Landgraf at the Max-Planck Institute of Psychiatry, both of whom had developed in-house oxytocin radioimmunoassays. Perplexingly, none of us met with success. A postdoctoral fellow in the lab, Alex Lee, said: "Why not just send samples out for sequencing?" I was more desperate than dubious, and since sequencing only cost $7 per sample, I figured we might as well be thorough. A few days later, Alex burst into my office: squirrel monkeys, and as it later turned out, multiple New World monkey species, had a novel form of oxytocin! This mutation arose from a substitution of a leucine for a proline amino acid at position eight; the molecule was transcribed and translated properly. Findings from this genetic work revealed why our oxytocin quantification attempts had been unsuccessful in squirrel monkeys, and helped dispel the widely-held notion that a universal form of oxytocin exists in all placental mammals [45].

My work on oxytocin's prosocial, anti-stress, and anxiolytic properties drew me increasingly to clinically relevant human subjects' research. I completed several studies with Alan showing that oxytocin biology was indeed dysregulated in patients with depression [46,47]. I also formed a collaboration with Allan Reiss, a child psychiatrist at Stanford, involving Fragile-X patients. The canonical triplet repeat expansion impairs FMR1 expression and leads to social deficits, anxiety, and enhanced HPA axis activation. Based on preclinical findings, we knew that Fmr1 gene knockout mice had diminished hypothalamic oxytocin production [48]. Our team exploited this information to show in a small pilot trial that intranasal oxytocin administration to Fragile X patients enhanced eye contact and diminished circulating cortisol concentrations [49]. I found that I loved the immediate relevance of conducting clinical research, and decided that it needed to be a core part of my research portfolio.

5. Faculty transition and introduction to autism

During my postdoctoral training, I met and married my husband, Laurence. As I initiated my faculty job search, Laurence and I agreed to keep an open mind regarding our future geographical location, and after a lengthy multi-institution job search, I was fortunate to be recruited to stay at Stanford. The San Francisco Bay Area was also an attractive option for Laurence, a tech executive. I began exploring new lines of research, with an eye toward establishing intellectual independence from David and Alan, a critical step for career advancement.

Autism was then receiving increased research funding due to federal lobbying efforts by stakeholder parents and the launch of the Simons Foundation Autism Research Initiative. A Stanford autism working group was quickly established to capitalize on these new funding opportunities. I was invited by Carl Feinstein, then division chief of child and adolescent psychiatry, to speak to the group on neuropeptide biology and its potential role in autism. As I prepared my slides, I was astonished by how little was known about autism's neurobiological underpinnings. Carl had been a clinician and co-author on the first study to investigate blood oxytocin concentrations in children with autism [50]. I began attending the autism working group and adopted Carl as a mentor. He was a kind and encouraging presence during my first years as an assistant professor. He also taught me about autism and urged me to study it. Carl later introduced me to Antonio Hardan, a child psychiatrist and autism researcher, after Antonio joined our faculty. Antonio and I soon found ourselves designing a study to test the popular, but not yet well interrogated, oxytocin-deficit hypothesis of autism. This would be the first of many exciting projects Antonio and I would conduct together, coordinated by the talented Robin Libove.

Another important collaborator, Joe Garner, was hired at Stanford a few years later. I had interviewed Joe as part of his faculty recruitment, but it was not until we found ourselves attending a quarter-long Team Science workshop that we meaningfully connected. We were sitting together when a facilitator raised the topic of statisticians. I lobbed the first grenade: There was a woefully insufficient number of statisticians available to consult on (let alone implement) appropriate statistical analysis plans to meet the demand, thereby impeding scientific progress. Joe piled on: Even when available, statisticians often did not understand fundamental biological principles, thereby contributing to false negative outcomes and the reproducibility crisis. I was reminded of a scene from the American movie, Step Brothers, where Will Ferrell and John C. Reilly's characters realize they effectively share one mind: "Did we just become best friends?!" they shout in glee. Joe and I were equally mortified and amused when the chair of a statistical unit interrupted us to unleash a diatribe about entitled biologists. Joe and I began sitting together throughout the quarter, safely out of earshot of the statistician, plotting ways to work together. I soon learned that Joe's remarks had not been idle criticism: He had been dually trained as a biologist and statistician, and was also a leading authority on translation and reproducibility. I invited Joe to help analyze the complex oxytocin and autism dataset that Antonio and I had recently generated, and with which we were currently grappling.

With Joe capably installed at the statistical helm, we found that blood oxytocin concentrations were highly heritable within families and that variation in oxytocin biology (oxytocin peptide concentrations; oxytocin receptor gene variants) contributes to important individual differences in human social functioning, including the social deficits that characterize autism [51]. Prior oxytocin treatment trials in autism had produced equivocal results [52–57], potentially because of variability in patients' underlying oxytocin biology. The relevance of such variability was reinforced by findings from rodent models of human syndromes with high autism penetrance (e.g., Fragile-X syndrome, cortical dysplasia and focal epilepsy syndrome, and Prader Willi syndrome) which had reported social impairments and diminished hypothalamic oxytocin-producing cell numbers [48,58,59]. Brain oxytocin reduction was associated with lower blood oxytocin concentrations in gene-edited animals, with social impairment ameliorated following oxytocin treatment [58,60]. These preclinical findings suggested that the oxytocin signaling pathway may be a promising therapeutic target for idiopathic autism, particularly in those with oxytocin signaling deficits. Our group was the first to empirically test this hypothesis: When pretreatment blood oxytocin concentration was included in our statistical model, oxytocin vs. placebo treatment significantly enhanced social abilities in children with autism, and individuals with the lowest pretreatment blood oxytocin concentrations improved the most from oxytocin treatment [61]. These findings revealed a compelling personalized medicine component to oxytocin treatment (i.e., there may be a subgroup of oxytocin deficient patients who stand to maximally benefit).

Our pilot findings also had important implications for accurately testing oxytocin's therapeutic potential in people with autism. We tried to secure follow-up support from NIH to perform an *a priori* biomarker-stratified trial, but NIH had funded a multi-site phase III oxytocin clinical trial (i.e., SOARS-B), and we were told to wait for its readout. This trial faced many logistical and other challenges. Disappointingly, the trial's primary outcome measure was negative [62]. Although the sites did collect pretreatment blood samples, oxytocin concentration did not predict treatment response. Endogenous oxytocin is labile and requires fastidious care in its collection, handling, processing, storage, shipment, and quantification [63]. Even small protocol deviations, which are more

likely to occur when multiple sites and labs are involved, can alter concentrations of measured oxytocin. It remains unclear to me whether chronic oxytocin treatment truly confers no benefit for autism, or it does, but the "signal" was not detected in the SOARS-B trial, for a myriad of reasons. I still wonder if autistic individuals with known endogenous oxytocin deficits might benefit from daily oxytocin "replacement." We may never know the answer, unless researchers outside the US conduct a biomarker-informed oxytocin treatment trial, or a philanthropist in the US steps forward to provide the necessary funding. Following the failed SOARS-B trial, there no longer appears to be federal support for this research.

There was a silver lining to this oxytocin and autism story. Our research measuring oxytocin concentrations in relationship to human socioemotional functioning [47,51,61,64–66] prompted private practice and academic clinicians, family stakeholders, and various patients to contact me to inquire about availability of oxytocin measurement for a broad range of disorders (e.g., craniopharyngioma, germinomas, septo-optic dysplasia, Prader-Willi syndrome, inherited central diabetes insipidus), in which social cognition and social interaction impairments are often prominent symptoms. In a few instances, people described to me near-overnight onset of autism-like symptoms following surgical resection in the hypothalamic region where oxytocin is produced. Indeed, insights gleaned from such correspondences inspired me and some clinical collaborators to launch several research initiatives in disorders with disease-induced disruption to hypothalamic oxytocin production [67,68].

6. Developing a primate model of naturally occurring social impairment to drive streamlined translation for autism

Although patient studies were certain to yield important information, progress in detecting and treating autism nevertheless was being impeded by the extraordinary difficulty of obtaining brain-relevant tissues from patients to study disease biology directly, and the absence of tractable face and construct valid animal models. These limitations underscored to me the tremendous value in developing an Old World monkey model of social deficits with more reliable behavioral and biological homology to the human condition [41].

Because autistic traits are common, highly heritable, and continuously distributed across the general human population, I sought a collaboration with John Capitanio, a professor at UC Davis, and a core scientist at the California National Primate Research Center (CNPRC), to develop screening tools that would enable us to identify and study naturally low-social rhesus monkeys (*Macca mulatta*) in CNPRC's large outdoor colony (N = 4000). Together with our team (including the exceptional Kate Talbot and peerless Laura Del Rosso), we found that naturally low-social male monkeys initiated fewer affiliative interactions, displayed more inappropriate social behavior, incurred more traumatic injuries, and exhibited a greater burden of autistic-like traits measured by a clinical autism screening scale we reverse-translated and validated for monkeys [69–74]. We also developed the first primate social behavior test battery with direct relevance to core autism symptoms (the construction of which had been informed by conversations with autism clinicians). Such tools are enabling us to better characterize the range and severity of social impairments exhibited by low-social animals. With an eye toward identifying "at-risk" monkeys, we also found behavioral markers (e.g., poor face recognition ability) in infancy that predicted, with 100% accuracy, whether an animal will become low-social years later [71].

Since there were no robust neurochemical markers of autism, we next interrogated in our model several biological systems that had strong rationales as candidates [70]. Our measures included the neuropeptides oxytocin and vasopressin and their receptors [48,75], as well as two kinase signaling pathways, RAS-MAPK and PI3K-AKT [76,77]. Using a statistical winnowing strategy, we found that cerebrospinal fluid (CSF) vasopressin concentration (but no other biological measure) was a key predictor of group differences in rhesus monkey social functioning. As would be expected of a putative biomarker, we also found that CSF vasopressin concentration was stable within individual monkeys over time [70], including across the breeding and non-breeding seasons [78]. These findings led us to test a critical hypothesis: If CSF vasopressin concentration is a neurochemical marker of quantitative variation in social functioning, individual differences in CSF vasopressin concentration should predict individual differences in both prosocial behavior and social impairment. This was indeed the case, as CSF vasopressin concentration positively predicted time spent in social grooming [70], and negatively predicted autistic-like trait burden [78].

These findings were fascinating to me, as I had long viewed vasopressin to be the unjustly neglected sibling of fair-haired oxytocin. It was vasopressin (not oxytocin) that was first implicated in pair-bonding and parental care in male mammals [12]. I had included vasopressin as a neurochemical of interest in our monkey research because my most profound experience as a graduate student had been administering vasopressin directly into the brains of male meadow voles, and watching it "turn on" paternal behavior [24]. I did not believe it to be a coincidence in the slightest that we were observing a link between low CSF vasopressin concentration and social impairment in an animal model of a disorder that impacts approximately four times as many males as females. Perhaps vasopressin would have its day in the sun after all.

7. Advancing detection and treatment of autism

My team next sought to translate our biomarker findings to people with autism. We had not observed a biological signal in the blood of low-social monkeys, however, and our preclinical findings indicated we would need to collect human CSF. Joe began referring to our study planning efforts as "project love child": I was passionate about birthing this study. Funding agencies, unfortunately, were not as enthusiastic. Our grant applications scored high on significance and innovation, but got eviscerated on research strategy. The aims were viewed as being too ambitious and too risky, and reviewers doubted we could collect sufficient CSF samples to test our hypotheses.

I often tell trainees and early career faculty that the best predictor of a successful scientist is their ability to get up off the floor after being kicked in the teeth. I vehemently disagreed with our reviewers: Just because collecting CSF was difficult, did not mean it was impossible. I had never been one to shy away from a challenge, and if there was a path forward, I would find it. I began reaching out to every pediatric clinician I knew at Stanford and elsewhere, conscripting them to help in our efforts. Two pediatric neurologists, Elliott Sherr at UC San Francisco, and Sonia Partap at Stanford, were particularly helpful in mapping out a strategy to obtain "extra" and "leftover" CSF samples from children undergoing standard of care lumbar puncture. Supported by cobbled together high-risk/high-reward institutional and philanthropic funds, we assembled a small "proof of concept" autism cohort [70]. Remarkably, we found that CSF vasopressin concentration was significantly lower in children with autism versus controls and that we could correctly classify 93% of individuals by just knowing their CSF vasopressin concentration. We found no group differences in CSF oxytocin concentrations.

We next sought to replicate this finding in an independent sample [79]. Although our first cohort had been a sample of convenience (i.e., they were recruited during medical procedures requiring CSF collection), the autistic individuals in our second cohort were well-characterized, medically healthy boys and girls who had undergone lumbar puncture as part of a research study [80] conducted by Sue Swedo, an NIH intramural investigator. In light of our prior findings, Sue readily agreed to collaborate with us. Led by senior research scientist Özge Öztan, an extraordinarily talented molecular biologist on my team, we again found that CSF vasopressin concentration in this much larger pediatric cohort identified autistic children with high accuracy, and boys with the lowest CSF vasopressin concentrations had the greatest

social symptom severity [79]. Although I had held out slight hope that we might observe lower CSF oxytocin concentrations in girls with autism compared to controls, this was not to be the case.

As an initial step in establishing the causal direction between vasopressin and autism, we next used infant CSF samples to conduct a quasi-prospective test of whether this association held true before the developmental period when autism first manifests [81]. This study exploited a rare archival collection of frozen "leftover" CSF which had been collected during medical care of febrile neonates. This archive had been assembled by John Constantino, then at Washington University in Saint Louis. I had learned about the existence of this archive over dinner with John at an autism meeting in 2010. We agreed that once I had sufficient proof from our symptomatic children, we could begin a collaboration. With this evidence at hand [70,79], John and his team reviewed thousands of paper medical records, traced the ones they could to electronic ones, and verified through 12 years of age, individuals with and without autism. John sent us his samples, and Özge quantified them. Although both Özge and I are fanatical about blinding and controls, we knew the answer to the study as soon as the data came off the plate reader: Individuals subsequently diagnosed with autism had significantly lower neonatal CSF vasopressin concentrations compared to those who did not later receive an autism diagnosis. The associations were specific to vasopressin, as neonatal CSF oxytocin concentration did not differ between infants later diagnosed with autism and those who developed typically. These findings suggested that a previously identified neurochemical marker of autism may be present early in life, before behavioral symptoms emerge, and that it may be useful for identifying and monitoring infants at risk for poor social outcomes.

This and other [82] evidence suggested that the vasopressin signaling pathway warranted consideration as a drug development target. On the strength of our CSF biomarker findings, Antonio and I launched a double-blind, randomized, placebo-controlled phase IIa pilot trial. We found that intranasal vasopressin treatment markedly enhanced social abilities in children with autism, as assessed by parent report, clinician evaluation, and child performance on lab-based tests. Vasopressin was also well tolerated with minimal side effects [83]. We are currently conducting a phase IIb vasopressin treatment trial in children with autism, using a dose found to be effective in our pilot trial. If our findings are replicated in the larger trial, vasopressin may have promise as a novel therapeutic intervention for a patient population that currently lacks a pharmacological strategy for its debilitating social behavior symptoms.

8. Achievements, work-life balance, and being a woman in STEM

I am now a tenured full professor at Stanford University. In addition to my research activities, I currently lead my department's major laboratories steering committee, where some of the world's leading translational psychiatry research is being conducted. I also serve as associate chair for research strategy and oversight in my department. In this capacity, my department chair, Laura Roberts, entrusted me and David Hong, associate chair for clinical research, to lead the emergency response team tasked with overseeing the cessation, and subsequent reinstatement, of research activities for more than 130 department PIs during the early days of the SARS-CoV-2 pandemic. It was a chaotic and terrifying time. Our work was difficult and all-consuming. Many, many millions of federal research dollars were at stake, as were our colleagues' research programs. We often joked - in a gallows humor sort of way - that we were "building the airplane as we were flying it." Now, many months removed from the pandemic, I am exceptionally proud of how our team steadily flew this hastily built airplane through the center of a raging storm, to arrive safely on the other side.

I am often asked how I balance my research activities and administrative duties with being a mother to three boys. This is not an easy question to answer. The short version is that it is hard work. I run my household and lab in a manner that would make a Prussian military general proud, and during the critical early years of my career, did not let anyone limit or define me. The longer version is more complicated. I was exposed to STEM as a child, by a father who never once discouraged his daughter from pursuing it. I had a loving, supportive mother who later went back to graduate school, not once but thrice, to earn an MBA, MSW, and PhD. My aunt was a thought leader in her research field and encouraged me to believe that one day I might be as well. My PhD mentor had a husband, two children, and a full life outside the lab. Terri was unapologetic on the occasions when she had to reschedule a work obligation to attend to a pressing personal one, but she never used her children as an excuse to let promises go unfulfilled, and she always got the work done. She was my blueprint for being a successful scientist and mother, as were other senior women along the way, notably: Bobbi Low, Sue Carter, Megan Gunnar, and Ruth O'Hara. I have also benefited from the enormous support of my department chairs: Alan Schatzberg, Laura Roberts, and Sherril Green. I have a loving husband who is an active and committed parent, and we were exceedingly fortunate when the boys were young to have nannies (Alvina, Maritza, Rachel, and Annie) who became honorary members of our family, and who still dearly love our children. Finally, I have long suspected that being in a pediatric field was more conducive to work-life balance. My pediatric-trained collaborators are dedicated parents, and I received nothing but enthusiastic support from them as I created my own family.

Not all of my experiences as a woman in academia have been positive, of course. Similar to the concept of allostatic load in stress neurobiology [84], I bear the cumulative "wear and tear" of repeated exposure to casual misogyny. More times than I can count, I have been interrupted by men who felt compelled to explain my own research to me, or who, during a committee meeting, parroted what I had said 15 min prior, often in what seemed to me a less articulate but louder manner. A male colleague once told others that the reason I was offered a faculty position at Stanford was because I was a woman. Another time, I sent an email to the (male) director of a core concerning a collaborative project I was conducting with a junior (male) colleague. The salutation on the return email read: "Dear Karen and Dr. X". More recently, I was invited to deliver a plenary talk at a conference. There were also smaller breakout rooms where others were speaking. I approached the audiovisual (AV) booth and politely requested to load my talk and review it. The AV technician told me that he was busy, but when my boss arrived, he would make time to handle it. I was initially confused; Laura was not attending this meeting. As awareness dawned, I informed him that I was, in fact, the speaker. He looked at me, and then said dismissively: "You must be in one of the breakout rooms." It was only once I deliberately helped him link the name on my badge to the one on the agenda that he grudgingly conceded to let me run through my slide deck.

A more insidious form of discrimination is the one that women reserve for each other. Early on, I was warned by multiple senior women that having children would derail my career. I would be relegated to the "mommy track," they said. These were often childless women, who had delayed having a family until it was no longer possible, or had foregone having children out of perceived necessity. They had clawed their way to the top under what I can only imagine were egregious circumstances, but had no intention of making the way easier for those of us who followed. When I became a mother, I noticed that several of these women would make a point, always within earshot of senior men, to inquire after my children. Once, I was in the lobby of a conference hotel, talking to three senior male colleagues. One of these women abruptly interrupted our conversation to ask: "Karen, how are your children?" The four of us looked at her askance. It was a bizarre and completely out-of-context question. One of the men mercifully and kindly responded: "Her boys are wonderful! But we were actually talking about Karen's fantastic new paper. Have you read it yet?" Having not received the intended reaction, this woman stormed off. I would like to think that this sort of behavior is decreasing, and I do think it is. Yet, not long ago, I received an urgent call from a medical resident. She knew of a PhD student who

was perilously close to quitting her program after a female professor had told her: "You can be a real scientist, or a mommy. Choose wisely." I agreed to speak with this distraught student from one of my children's soccer practices, and calmly reassured her that it was indeed possible to be both. I hope she stays the course.

The leaky pipeline is real. Even having trained at institutions like Michigan and Stanford, nearly every one of my female peers, for one reason or another, has left academia. The time and energy I invested in nurturing these relationships, with aspirations of one day trading well-trained students and collaborating on research projects, never paid off. The same phenomenon did not happen to my male colleagues, who I often wistfully observe greeting one another at meetings, reliving their graduate school and postdoctoral exploits. Such is another and frequently overlooked loss for female scientists: The costly pruning of our professional networks. I have, however, met other women along the way, many also the last of their cohorts, who have become cherished colleagues and friends. I am looking at you, Karen Bales, Suma Jacob, Kati Gothard, Shelly Flagel, Annie Penn, Mar Sanchez, and Cathy Crockford.

Many paths are available to get us where we need to go. I am no longer surprised that my career has come full circle, from finding neuropeptides through Darwinian medicine, more than 25 years ago. As a researcher, I have made my career in a medical school and spend much of my time with clinicians. You might say that I have become a monkey psychiatrist, of sorts. Had things played out a little differently, I may have been an actual psychiatrist, or perhaps, a pediatric neurologist. But I do not think my career would have been substantially different. I would have still been driven toward discovery, and trying to make the world a better, kinder place.

To the young women reading this piece, I hope you dream big, ambitious dreams. Do not let anyone limit or define you. When you begin to falter, or lose confidence in yourself, draw strength and courage from the wise words of Hall of Famer Wayne Gretzky: You miss 100% of the shots you don't take.

Declaration of competing interest

The Board of Trustees of the Leland Stanford Junior University has filed patent applications related to data reviewed herein: PCT/US2019/019029 ("Methods for diagnosing and determining severity of an autism spectrum disorder") and PCT/US2019/041250 ("Intranasal Vasopressin Treatment for Social Deficits in Children with Autism"). These patents have not been granted, nor licensed, and the author is not receiving any financial compensation at this time.

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