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I am writing this letter providing my strongest support of Dr. Stephanie Jones in her potential appointment as an Assistant Professor. Steph is a truly great scholar, whose work is based in high-level expertise in applied mathematics, and requires high-level expertise in neuroscience. This kind of blending of cutting edge fields is for me the mark of an innovative thinker. Being able to collaborate with Steph has been transformative for my own research—her unique abilities and insights have opened up new directions at many turning points. While her research profile is much larger than our shared efforts, I value her contribution to my work as being the most beneficial collaboration I have ever engaged in.

This letter has 4 parts: First, I discuss Steph's distinctive merits as a scholar; second, I discuss my collaborative work with her; third, I discuss my view of her potential for career growth; and, fourth, I discuss my opinion of her as a departmental citizen and teacher.

Part I: Scholarship

Steph is a fantastic scholar with a unique combination of skills. She is intensively trained in mathematics (the discipline of her doctorate) and in the applied merger of math with experimentation (the focus of her K-award). Her mathematics training is in computational modeling based in principles of dynamical systems, with biophysically accurate modeling of multi-neuronal circuits her area of greatest expertise.

Her experimental expertise is in the acquisition and computationally rigorous analysis of human magnetoencephalographic (MEG) recordings, typically obtained from subjects during presentation of sensory stimuli and performance of psychophysical tasks. While this is her area of greatest distinction, Steph has also worked extensively with experimentalists who use reduced approaches (typically electrophysiological recording in animal models) and is fluent on many details in that domain as well.

This kind of combined depth in multiple fields is rare, and positions Steph to have impact on many areas of scholarship. One index of her skill in these domains is that she is regularly called on as a reviewer for both high-level mathematical work and neuroscience. She is one of the rare individuals who can have a conversation on the detailed nuances, frustrations and power of both approaches as applied to understanding the brain.

While expertise is essential to success as a productive scientist, it is also obviously not the only skill required. One must also be able to produce meaningful ideas that advance the field. Steph is a truly generative scholar, who produces exactly such hypotheses.

Her most prominent success is probably her construction of a computationally detailed model of the neocortex that can explain evoked responses and oscillatory patterns in the MEG. This neocortical model includes multiple cell types (pyramidal cells and interneurons), multiple layers with realistic interconnectivity, and multiple extrinsic inputs (e.g., thalamic and intracortical). This conceptual tool allows her to manipulate independent cell types, connectivity and biophysical details such as expression of different channel types to query the underpinnings of these complex MEG signals in humans.

With this novel approach, she has been able to systematically predict the relation between spiking or subthreshold activity in a specific cell type and MEG measurements from the surface of the human head. This precision is a remarkable achievement, and the success of this model in predicting evoked responses (Jones et al., 2007), oscillations (Jones et al., 2009) and neurophysiological changes with normal aging (Ziegler et al., 2010) indicate the power of this tool and, more importantly, the power of the kind of approach. **Steph is *the* leader in applying mathematically rigorous approaches to understanding MEG signals, a distinctive accomplishment to already be at the top of this area at this point in her career.**

Her work has also been generative in allowing inferences in the other direction, from complex human signals to detailed network activity in animals. As I will discuss below, her recent work modeling human signals led us to an entirely novel theory of how thalamocortical interactions may generate beta oscillations. Without her modeling, an entire series of studies in my lab—and a grant we recently received funding for—would never have gone forward.

In summary of this section, Steph is a great scientist. I have had many collaborations with computationally savvy scientists (or mathematicians or engineers), and I have mentored many as well—at one point, my laboratory only contained ex- mathematicians and physicists, despite being a neuroscience lab. Despite the remarkable training and skill sets may quantitatively trained individuals have, they often fail to gain the traction they should in realizing real gains in knowledge. Translating mathematical skill into real neuroscience progress is a surprisingly rare art, in part because it takes expertise in multiple fields, in part because it takes the social skills to interact with many kinds of collaborators, and in part because it takes someone who is absolutely dogged in pursuit of a meaningful advances in understanding the brain, not just interesting algorithms. Steph is the rare scholar who has all these traits, allowing her to apply her great quantitative skills productively to interpret and inspire meaningful experimental insight.

II. My Collaborations with Steph

Our first project began when we were both postdoctoral associates at Harvard Medical School/Massachusetts General Hospital, and grew out of conversations over lunch about the dynamics of neural networks. My collaborations with Steph have occurred in two domains. First, she has played a key role in generating models that help us interpret our animal data. These models provide novel mechanistic interpretations of the dynamics expressed in neocortex.

Our first collaboration (Garabedian, Jones et al., 2003) yielded a model that made novel experimental predictions regarding sensory-driven adaptation, one of the most intensively studied topics in systems neuroscience. Her work predicted that, contrary to the dominant view, an inhibitory interneuron-dependent form of suppression was likely underlying important aspects of the spiking patterns we observed. She specifically predicted that this inhibition should facilitate with increasing frequency of sensory stimulation, and should have a longer time constant than typical GABAergic inhibition. We just finished a new study (Knoblich et al., 2011 *COSYNE Abstracts*) that has discovered this novel form of inhibition driven by higher-frequency sensory drive that she predicted must exist 8 years ago.

This kind of insight is, needless to say, priceless in the pursuit of mechanism. In this case and in many others, in her attention to capturing all aspects of the experimental phenomena, she was compelled to propose a mechanism contrary to the existing dogma. Specifically, most neurophysiologists view sensory adaptation as purely dependent on synaptic depression, not on enhanced inhibition. Steph ran counter to this view in her model and that hypothesis has now been substantiated with detailed experimental data.

This kind of collaboration—making models to explain data from animal models—has also recently been fruitful in the explanation of data from recent optogenetics papers (Cardin et al., 2009, 2010). That paper showed that driving a specific interneuron type with light induces a “gamma” rhythm, a resonant oscillation at ~40 Hz. While a decisive finding, this result was not surprising given the wealth of prior modeling data predicting it. What was more surprising was that selective optical drive of excitatory cells in a ‘control’ mouse led to enhancement of lower-frequency rhythms (most prominently “alpha” rhythms at 8-16 Hz). In collaboration with a postdoctoral associate we are co-mentoring, Steph developed a model that could provide both forms of enhancement in the same neocortical circuit (Vierling-Claassen, Cardin, Moore and Jones, 2010). Again, this modeling has yielded a list of experimental predictions we are eager to test.

The second kind of collaboration we have engaged in has focused on MEG recording and human psychophysics (e.g., Jones et al., 2007; Jones et al., 2009; Jones et al., 2010). As I mentioned above, this area is one in which Steph is the leader in applying mathematically interesting and rigorous analysis to understanding these signals.

Recently, my collaborations with Steph have come full circle, with her modeling of human data guiding our animal work—providing a direct ‘translational’ link between levels of analysis. This progress is best exemplified by her recent work on beta oscillations (15-30 Hz). She has found (Jones et al., 2010) that expression of beta oscillations prior to arrival of a sensory stimulus provides a consistent prediction of perceptual success (the detection of a threshold-level tactile input). Other work has shown that alterations in beta are a robust clinical marker in Parkinson’s disease. In sum, all signs suggest that beta has computational import, or is at least a consistent concomitant of processes that do.

In studying the human beta rhythm we observed in MEG, Steph found that the only model that captured all of the phenomena we observed ran strongly counter to conventional views of beta emergence (Jones et al., 2009). Specifically, she found that the classic view—which depends on the time constant of intrinsic currents in pyramidal neurons to set the rhythm—could not capture the observed phenomenology in humans. She instead found that a specific pattern of activation in different kinds of thalamic nuclei was necessary, which then converged on the distal dendrites and somata of neocortical pyramidal neurons.

Steph’s modeling of human data led us to perform experiments in mice, using optogenetics to selectively drive thalamic nuclei that target either the distal dendrites or the soma. These new data provide direct support for her novel theory of beta emergence. This kind of success, while preliminary still, is exactly what one would hope for. Steph used computation to bridge human and animal studies, and this use of the model led to an entirely new view of beta emergence. This kind of approach is what I meant above when I said that Steph is truly generative—through her computational strength, creativity and attention to detail, she finds new hypotheses that have the depth and specificity to be truly important.

I want to emphasize a few more points with regard to Steph's recent work on beta. If she is correct, this hypothesis provides an intuitive and direct explanation for the alterations in this rhythm in Parkinson's disease. As such, her model also explains why microstimulation in these patients is so effective at reducing beta expression. Given that such a reduction in beta is a strong correlate of their probability of recovery, this model may be a significant clinical advance. As I mentioned above, her theory is the basis of a recently funded grant from the National Science Foundation, and will be the basis of further applications to Parkinson's disease focused funding sources.

In summary of this section, my collaboration with Steph has had a fantastic positive impact on my thinking and on the experiments performed in my laboratory. She has generated multiple novel mechanistic hypotheses that emerged from trying to understand data, and have returned to in turn influence new experiments.

III. Future Career Directions

While Steph has already had a wonderful impact on the field and my laboratory, she is now at a particularly strong point in her trajectory, coming into what will be the most productive years of her career. She has now had enough success that she is getting the necessary recognition to get full traction—she is regularly invited to speak in America and Europe, and is sought after as a key reviewer/Chapter writer in her areas of expertise. Her existing theoretical progress and acknowledgment in the field for her neocortical modeling have ideally positioned her for expansion into novel domains.

The first domain she is expanding into is clinically relevant studies. In addition to her work in Parkinson's Disease described above, also important in this regard is her work with Children's Hospital in Boston looking at MEG recordings from infants and children. She is using her model to understand the progression of changes in MEG signals with development, for example trying to understand signals from children with heritable developmental abnormalities in neocortical layer V pyramidal cells (the neuron type that is the primary engine for the observed MEG activity). This kind of application of her model—to understand longitudinal changes in brain activity—has already proven useful in studying normal early aging (Ziegler et al., 2010).

She is also expanding her tool development to include modeling other complex neurophysiological signals in addition to MEG. Specifically, Steph is now beginning to try to understand the local field potential ("LFP"). Her model is currently being spatially elaborated, allowing neuron-specific and column-specific predictions as to the origins of activity patterns recorded across grids of electrodes. **If she can solve the LFP signal with the same success she had in solving MEG, the tools she produces for making these calculations will transform systems neuroscience.** There is currently *no* believable and detailed model for the biophysical origins of these signals, despite the fact that they are used by many laboratories and in many clinical settings. Building such a tool would continue her series of transformative area of impact on this field.

IV. Steph as a Colleague

Steph is a wonderful colleague. In addition to being (very) smart, she is friendly, attentive, and highly supportive of students and co-workers. While these comments are obviously subjective, I think it matters in considering a faculty-level appointment that the person will be a good (or, as I anticipate for Steph, a great) departmental citizen. This matters especially for a scholar whose work is often at the intersection between fields, meaning they need to work well with others. Steph fits the bill on all counts: She listens well, has real enthusiasm for people and for the work in all of its many details, and seeks out opportunities to interact.

While not necessarily relevant to her role as a research faculty member, I will point out that Steph is also a strong teacher. She taught in a graduate course I directed on Neural Dynamics at MIT in 2008, and did a great job lecturing and mentoring students. Her friendly personality and general empathy for others made her a natural in this regard. I have also seen her act as a research mentor and co-mentor of graduate and postdoctoral students, and she also has had great success in this regard. Her diverse trainings give her a wealth of knowledge and experience to relay, and she does so with persistence and a real compassion for helping students achieve their goals.

In overall summary, I am a huge fan of Steph, and it is my hope that this appointment will be awarded. This desire is in part entirely selfish—she is a fantastic scholar who has repeatedly had a major impact on my work, so finding a secure path for her at Brown would be wonderful from that perspective. That said, this desire also reflects more generally on my high opinion of her: Brown would be a wonderful situation for her. She will be immersed in a top rate department where she can interact with leading colleagues in her field and great students.

I am also of the opinion, as I hope is obvious, that Brown stands to gain significantly from her appointment. Most importantly, above and beyond specific contributions she can make, Steph is a great scholar and person who would enrich any environment with the perspectives she provides and her enthusiastic presence. Providing her with a secure home could, given her success, be key to keeping her in this environment, which I think would be a great decision.

If I can be of any further assistance, please do not hesitate to contact me,

Yours,

Christopher Moore, Ph.D.