Sir, We would like to thank Dr Rosenkrantz for her interest in our recent paper on physiological differences between patients with psychogenic and organic forms of limb dystonia. We are also very grateful for the opportunity to discuss in detail the connection between input–output relationships and effects of paired associative stimulation (PAS). It is a topic of some confusion among those who use transcranial magnetic stimulation and it is worthwhile exploring in detail possible connections between these two phenomena.

In the usual PAS experimental design, a standard transcranial magnetic stimulus is used to evoke motor evoked potentials in the abductor pollicis brevis muscle. Application of the PAS25 protocol increases the amplitude of motor evoked potentials evoked by this standard pulse for the following 30 min or so. In contrast, the input–output curve uses a range of transcranial magnetic stimulation intensities to plot the relationship between intensity and size of evoked motor evoked potential. As Dr Rosenkrantz points out, if the effect of PAS25 is equivalent to increasing the intensity of the transcranial magnetic stimulation pulse, then subjects who have a steeper input–output curve will achieve a greater increase in amplitude of motor evoked potential than those with a shallow input–output curve.

However, first it is important to underline that proposing PAS25 to be the same as increasing the intensity of the transcranial magnetic stimulation pulse is not equivalent as saying that the effect is the ‘same’ as increasing transcranial magnetic stimulation intensity. Measurements of the strength-duration properties of transcranial magnetic stimulation indicate that it stimulates axons; turning up stimulation intensity increases response size because more axons are recruited at higher intensities. For PAS25 to have the ‘same’ effect we would have to propose that PAS25 increases the excitability of axonal membranes, so that more axons are stimulated by the standard transcranial magnetic stimulation pulse after a PAS25 protocol. This may be a remote possibility, but seems unlikely in view of the fact that there is good evidence that PAS25 involves changes at glutamatergic synapses.

Indeed a much more consistent hypothesis is that PAS25 does not affect the number of axons stimulated, but instead it increases the effectiveness of the terminal synapses attached to those axons. This then could result in a greater total depolarization of a second set of neurons and a larger motor evoked potential response. In this case, from the point of view of the receiving neurons, the effect of PAS25 could appear equivalent to that of increasing the transcranial magnetic stimulation intensity: in each case they receive more depolarization. So how does this increased depolarization interact with different input–output slopes? The answer depends on the reason why the input–output slopes differ between groups of individuals.

Let us imagine two groups of subjects, one of which has a steeper input–output slope than the other. The slope of the input–output curve depends on the distribution of excitability at all levels of the corticospinal pathway. It could, for example, be increased because of an increase in spinal excitability. That is, the amount of depolarization reaching the spinal cord after a given stimulus could be the same in two groups of subjects, but in the group with higher spinal excitability this would discharge more spinal motoneurons than expected and the input–output slope would be steep. In this case, the effect of PAS25 on the cortex
could be the same in both groups but the motor evoked potential change would be larger in the group with the steeper input–output slope. This is presumably the scenario that Dr Rosenkranz has in mind when warning of the dire consequences of ignoring initial differences in input–output slopes.

However, there are other possibilities which do not yield the same answer. As we explain below, the general rule turns out to be that if PAS affects synapses ‘before’ the stage of increased input–output excitability, then the effect of PAS is equivalent to increasing the intensity of the transcranial magnetic stimulation pulse, as in the example above. In contrast, the effect of PAS will be unrelated to input–output excitability if it changes synapses ‘at’ or ‘after’ the stage of increased input–output excitability.

For example, if the input–output slope is increased because of increased excitability of the axons stimulated by transcranial magnetic stimulation, then if PAS25 increases the efficiency of their terminal synapses, it will have the same effect on the amplitude of the standard motor evoked potential no matter what the input–output relationship might be.

The same thing would happen if the excitability of the axons stimulated by transcranial magnetic stimulation is the same in each group of subjects but the input–output slope is steeper in one of them because their terminal synapses are more efficient. Thus, in the usual PAS25 protocol, the standard transcranial magnetic stimulation pulse is adjusted to produce a motor evoked potential of 1 mV. This means that the axons stimulated by transcranial magnetic stimulation deliver the same amount of depolarization to the corticospinal system in both groups (even though a smaller number of axons need to be stimulated in the group with the steeper input–output curve). If PAS25 increases the efficiency of these synapses by the same proportion in each group, then the effect on the standard motor evoked potential will be the same, no matter what the input–output slope.

The outcome is that it may not be appropriate to account for differences in the response to PAS by relating them to differences in the slope of the input–output curve. In circumstances similar to the last two examples above, such a correction could cancel out a true increase in the effect of PAS, creating a false negative. Perhaps the best conclusion is that changes in PAS are easier to interpret if initial input–output slopes are the same in two groups of individuals. If the slopes differ, then some caution may be required.

The lack of correlation between the input–output curve and PAS after effects is further corroborated by data on Parkinsonian patients. Indeed several publications suggest that patients with Parkinson’s disease have an increased input–output slope either ON or OFF L-Dopa treatment compared with controls (Chen et al., 2001). Despite this, motor evoked potential facilitation after PAS is abolished in the OFF condition while dopaminergic treatment re-establishes normal levels of plasticity (Morgante et al., 2006; Ueki et al., 2006). This therefore provides further evidence that after effects of PAS can be unrelated to changes in input–output excitability.

Finally, do input–output curves differ in steepness between patients with dystonia and healthy individuals? As Dr Rosenkranz points out, we did not compare this in the groups studied in our paper. We studied rare psychogenic patients over a long period, some before questions about input–output curves were common. However, the published literature suggests that input–output curves in organic dystonia may be similar to normal. The first of these, by Ikoma and colleagues (1996) focussed mainly on the effect of background levels of contraction on input–output slopes and found that contraction produced more facilitation of motor evoked potentials in patients with focal arm dystonia than normal. There is no specific mention in the text about the situation at rest (when PAS protocols are usually performed). However, Fig. 2 shows some data of motor evoked potential size at different stimulation intensities. They overlap in the two groups, suggesting that the input–output slopes would have been similar in both cases. A more recent study from P. Schwingenschuh et al. (Movement Disorders, in press) confirms this using more standard approaches.

There is one other feature of PAS in patients with dystonia that differentiates them from healthy controls, namely input specificity. In healthy subjects, the effects of median nerve PAS are largely confined to muscles innervated by the median nerve. In patients with writer’s cramp and musician’s cramp, PAS also increases excitability of nearby ulnar nerve innervated muscles (Quartarone et al., 2003, 2006, 2008, 2009; Weise et al., 2006). We have proposed that this is an important biomarker in dystonia (Quartarone et al., 2006, 2009).

Dr Rosenkranz also points out, quite correctly, that the present understanding of the mechanism(s) of short interval intracortical inhibition has led to a reappraisal of how to best compare levels of short interval intracortical inhibition between groups of individuals. In our article, we presented data that compared short interval intracortical inhibition at a single intensity of conditioning stimulus. However, Avanzino and colleagues (2008) have shown that short interval intracortical inhibition is reduced at a variety of conditioning intensities in patients with either psychogenic or organic dystonia. Indeed, half of the psychogenic patients included in our study were the same as those studied by Avanzino et al. (2008). Thus, it is likely that our results would have been similar if we had studied short interval intracortical inhibition in these patients at a variety of conditioning intensities.

In conclusion, we do not agree with Dr Rosenkranz’s proposal that changes in the effect of PAS between groups of patients should always be corrected for differences in the slope of input–output relationships. Such a correction could be flawed depending on the reasons for differences in plasticity and input–output slopes. We would instead encourage a more measured approach that acknowledges the difficulty in assessing PAS effects in circumstances where there are large differences in input–output slopes. In addition, we would point out that published data suggest that input–output slopes in patients with dystonia are the same as in healthy subjects.

References