

1 How does transcranial magnetic stimulation modify neuronal activity in the
2
3 brain? - Implications for studies of cognition
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Abstract

1 Transcranial magnetic stimulation (TMS) uses a magnetic field to “carry” a short lasting
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3 electrical current pulse into the brain where it stimulates neurones, particularly in superficial
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5 regions of cerebral cortex. TMS can interfere with cognitive functions in two ways. A high
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7 intensity TMS pulse causes a synchronised high frequency burst of discharge in a relatively
8
9 large population of neurones that is terminated by a long lasting GABAergic inhibition. The
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11 combination of artificial synchronisation of activity followed by depression effectively
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13 disrupts perceptual, motor and cognitive processes in the human brain. This transient
14
15 neurodisruption has been termed a “virtual lesion”. Smaller intensities of stimulation produce
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17 less activity; in such cases, cognitive operations can probably continue but are disrupted
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19 because of the added noisy input from the TNS pulse.
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26 It is usually argued that if a TMS pulse affects performance, then the area stimulated must
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28 provide an essential contribution to behaviour being studied. However, there is one exception
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30 to this: the pulse could be applied to an area that is not involved in the task but which has
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32 projections to the critical site. Activation of outputs from the site of stimulation could
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34 potentially disrupt processing at the distant site, interfering with behaviour without having any
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36 involvement in the task.
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41 A final important feature of the response to TMS is “context dependency”, which indicates
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43 that the response depends on how excitable the cortex is at the time the stimulus is applied: if
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45 many neurones are close to firing threshold then the more of them are recruited by the pulse
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47 than at rest. Many studies have noted this context-dependent modulation. However, it is often
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49 assumed that the *excitability* of an area has a simple relationship to *activity* in that area. We
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51 argue that this is not necessarily the case. Awareness of the problem may help resolve some
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53 apparent anomalies in the literature.
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Introduction

Transcranial magnetic stimulation (TMS) provides a method of stimulating human brain through the intact skull without producing significant discomfort (Barker et al., 1985). After its introduction in 1985, it soon became evident that TMS can be used to interfere transiently with cortical processing. For instance, TMS can suppress visual perception of briefly presented trigrams when a single TMS pulse is applied to the occipital cortex 80 to 100 ms after stimulus onset (Amassian et al., 1989). This type of disruptive effect of TMS on cortical function is often referred to as a “virtual lesion” (Pascual-Leone et al., 2000). Such effects are usually created by applying a single pulse or a short high-frequency train of stimuli to the cortical area of interest during an experimental task. The approach is now widely used in cognitive neuroscience to interfere with a wide range of brain functions, including perception, motor execution, or higher-level cognitive processes. The popularity of TMS as a means of studying perceptual and cognitive processes in the intact human brain contrasts with the limited knowledge about the mechanisms by which TMS disrupts brain function. The aim of this review is to summarize some important features of TMS and their implications for investigating brain-behavior relations with “neurodisruptive” TMS. This review only deals with the acute “online” effects of TMS on brain function. Regarding the physiology underlying the conditioning effects evoked by repetitive TMS we refer to recent reviews of this topic (Siebner and Rothwell, 2003; Thickbroom, 2007).

Basic principles of TMS

The basic principles of TMS have been covered in many excellent reviews (Amassian and Maccabee, 2006; Bestmann, 2008; Pascual-Leone et al., 2000; Ziemann et al., 2008). For the present purposes three features are important when considering the “virtual lesion” effect. First, the electrical pulse induced in the brain is very short lasting. A typical monophasic pulse

1 current rises to a maximum and has reversed towards zero in about 200 μ s. This leads to
2
3 highly synchronous activation of neurones.
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6 Second, the stimulation is not focal. With a circular TMS coil, the maximum electric field
7
8 induced in the brain lies in an annulus under the coil; to an approximation, coils wound in a
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10 figure of eight shape are equivalent to two circular coils in which the fields summate at the
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12 point of overlap. Thus they produce about twice the field under the junction region as at the
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14 edges of the wings, but even so the effective area of stimulation is still several square cm. It is
15
16 impossible to give an exact answer about the volume of tissue stimulated by any TMS coil.
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18 This depends on the geometry of the coil as well as the stimulus intensity and the electrical
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20 properties of the cortex under the coil (see below). However, if focality of stimulation is the
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22 aim then it is clearly desirable to use as low a stimulus intensity as possible to prevent
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24 inadvertent activation of distant structures.
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31 The third important feature of TMS is that the magnetic field (which induces electric current
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33 in the brain) falls off very rapidly with distance from the TMS coil. The exact relation
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35 depends on the size of the coil, but for a typical coil, the field at a distance of 4 cm may be
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37 only about 30% of that at the coil surface. This means that superficial areas of cortex are easy
38
39 to stimulate, but those deep in a sulcus or far from the scalp surface such as mesial temporal
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41 or frontobasal cortex have a much higher threshold. In fact even if it is possible to activate
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43 these structures at high TMS intensities, other areas that lie superficial to the intended site will
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45 be activated even more strongly, so that any behavioural effect will be difficult to attribute to
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47 stimulation of the deep structure alone.
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56 **How does the electrical field induce action potentials in cortical axons?**
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1 Experiments in the motor cortex have measured the strength-duration relationship of the
2 pulses that are needed to evoke EMG activity in contralateral muscles. This relates the
3 duration of the induced electrical current to the amplitude needed to evoke a response of a
4 given size. The form of the curve suggests that TMS stimulates axons, and not cells because
5 axons are most efficiently activated by a short duration pulse whereas cells require longer
6 pulses. Exactly which axons are stimulated is not known. However, whichever they are, it is
7 thought that excitation occurs in the grey matter of the cortex rather than in the subcortical
8 white matter (Edgley et al., 1997) since the former is nearer the scalp surface and has a lower
9 electrical resistance than the underlying white matter.

10 There is one other rule about excitation of axons that has unexpected consequences for TMS:
11 Stimulation occurs when the spatial derivative of the electrical potential (i.e. the “rate” at
12 which potential changes with distance) along the length of the axon exceeds a certain
13 (negative) value. Effectively, stimulation is most likely to occur when there is a large change
14 in voltage along the length of an axon. The result of this is that if an axon followed a circular
15 course exactly under a circular TMS coil, then it would never be activated since the electrical
16 field would be the same all along its length. The best way for it to experience a voltage
17 gradient would be if the axon were bent out of the circle at one point. Stimulation would
18 occur at the bend since this is the location of the maximum spatial derivative of the field.

19 In fact, experiments with single axons as well as theoretical calculations show that TMS is
20 most likely to activate axons at a point where they bend out of the electric field (Maccabee et
21 al., 1998). Since TMS coils induce electrical fields that are oriented in particular directions
22 under the coil it is easy to see that changing the orientation of the coil is very likely to change
23 the population of axons that are activated. This particularly applies to figure of eight coils
24 where the electric field is aligned parallel to the junction region, and can therefore be easily
25 rotated by rotating the coil.

1 The importance of the geometrical relation between the main orientation of the induced field
2 and the neuronal structures that are to be stimulated has been demonstrated both for TMS over
3 the hand area of the primary motor cortex ($M1_{HAND}$), and for TMS over the occipital cortex.
4
5 TMS of the $M1_{HAND}$ is most effective if the induced current in the brain runs approximately
6 perpendicular to the central sulcus in a posterolateral to anteromedial direction (Mills et al.,
7 1992). Similarly, the optimal current direction for stimulation of primary visual cortex to elicit
8 a visual phosphene occurs when the coil is oriented perpendicular to the gyrus under the coil
9 at the site of stimulation (Kammer et al., 2007). The observation that the direction of the
10 induced tissue current contributes to the efficacy of TMS is also relevant to “neurodisruptive”
11 TMS studies that target other cortical areas. For instance, the TMS-induced current
12 orientation had a significant impact on task performance when TMS was given over the
13 prefrontal cortex during a memory-guided saccade task, presumably because different
14 neuronal populations were disrupted at different current orientation (Hill et al., 2000).
15
16 In addition to these macroanatomical aspects, the microgeometry of each cortical neuronal
17 population and the degree of axonal myelination determine the susceptibility of a given
18 neuronal population to the induced electrical current. Interneurones with a short non-
19 myelinated axon and a large tree arbour are less susceptible than longitudinally oriented
20 pyramidal cells with a large-diameter myelinated axon and a dendritic tree located at the
21 opposite site of the soma to the axon.
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23 The bottom line is that it is still poorly understood which set of axons is initially activated by
24 the electrical field induced by TMS. Factors such as the degree of axonal myelinisation, the
25 cell type, and the presence of large bending axons are all known to have an important
26 influence. At the present time it is safe to conclude that the electrical field preferentially
27 excites the axons of a subset of neurones in the stimulated cortex.
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Influences on activity at brain regions distant from the site of stimulation

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4 There are two ways in which TMS at one site can influence activity at another site. First, the
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6 stimulus might directly change activity in axonal projections to other areas. This would lead
7
8 to synaptic activity in the target zone and directly change patterns of activity in that structure.
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10 The second possibility is more indirect. Many cognitive operations are processed by ongoing
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12 interactions within spatially separate networks of neurones. In such a case, TMS at one node
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14 in the network can lead to changes in distant zones even if they are not directly connected to
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16 the stimulus site. This is because changing activity at any site will have knock-on effects
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18 throughout the network.
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23 The fact that MEPs can be recorded in hand muscles after TMS of the M1_{HAND} is maybe the
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25 most obvious demonstration that focal excitation in the cortical target area does not remain
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27 confined to the site of stimulation. In this case, the stimulated area is at least two synapses
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29 distant from the muscle, and shows that regional excitation in the target area readily spreads
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31 within the nervous system via pre-existing neuronal connections in a network.
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36 Within the brain, cortico-cortical interactions via directly connecting pathways have been
37
38 successfully studied by stimulating two cortical motor areas with TMS (two-site TMS as
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40 opposed to single-site TMS). For instance, a TMS pulse given to one M1_{HAND} can influence
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42 the excitability of M1_{HAND} in the opposite hemisphere (Di Lazzaro et al., 1999; Ferbert et al.,
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44 1992). The effect may be facilitatory or inhibitory depending on the intensity of stimulation
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46 and is probably conducted via fibres in the corpus callosum since these interhemispheric
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48 interactions are absent after callosotomy. Cortico-cortical synapses are thought to be
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50 excitatory and glutamatergic, so that inhibitory effects are presumably mediated via an
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52 interneurone in the receiving cortex. The conclusion is that behavioural effects of a TMS
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54 pulse may be due not only to activation at the site of stimulation but also to direct inputs to
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1 remote areas of cortex. As at the site of stimulation, the mechanism of these remote effects
2 depends on stimulus intensity.
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6 At the network level, complex changes in activity patterns can be studied by analysing how
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8 TMS modulates oscillatory activity in the brain. Event-related EEG analysis shows that a
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10 single pulse of TMS induces a characteristic negative deflection at 45 ms (N45) and a
11
12 transient oscillation in the beta frequency-range (15-30 Hz) close to the stimulation site (Paus
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14 et al., 2001; Van Der Werf and Paus, 2006). It has been proposed that these oscillations reflect
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16 TMS-induced resetting of natural brain oscillators by the TMS pulse. Event-related coherence
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18 analysis revealed that single-pulse TMS enhanced coherence in the alpha band between both
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20 hemispheres within the first 500 ms after the pulse which was also interpreted in the context
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22 of resetting (Fuggetta et al., 2005). These studies raise the interesting possibility that some of
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24 the neurodisruptive effects of TMS may be related to the resetting of ongoing inter-regional
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26 network activity.
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32 **Interference with function**

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39 There are two main ways in which TMS could interfere with function: it could prevent
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41 activity by silencing neurones (the “virtual lesion”) or it could add extra “noisy” activity to
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43 ongoing processing. In practice it seems likely to be a combination of each, with the balance
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45 depending on the intensity of stimulation.
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50 Physiological studies have shown that a single TMS pulse to the M1_{HAND} area that is
51
52 suprathreshold for evoking a muscle contraction on the opposite side of the body produces a
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54 complex pattern of activity in the cortex. The initial effect is the induction of synchronised
55
56 high frequency discharges in pyramidal output neurones at frequencies of around 600Hz.
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59 These last for up to about 10ms and are followed by a long lasting GABAergic inhibition.
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1 The evidence for the former comes from recordings from epidural stimulating/recording
2 electrodes that have been implanted in the spinal epidural space of patients for the treatment
3 of pain and other conditions (Di Lazzaro et al., 2004). They show that a suprathreshold TMS
4 pulse produces a series of 4 or more descending volleys of activity, each separated from the
5 next by about 1.5 ms (i.e. about 600 Hz). These are thought to be analogous to the D and I
6 waves seen in recordings of corticospinal activity in animals after direct electrical stimulation
7 of the exposed cortex (Amassian and Cracco, 1987). The initial D wave, which is seen only at
8 high intensities, is the result of activation of corticospinal axons in the subcortical white
9 matter, whilst the lower threshold I waves that follow are the result of repetitive excitatory
10 synaptic inputs to the same neurones.
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25 Evidence for emergence of a large GABAergic IPSP comes from examining the effects if
26 TMS pulses are applied while the subject is maintaining a background contraction of the
27 target muscle. In this case, the MEP is followed by a period of silence in ongoing activity that
28 lasts 100ms or more (the cortical silent period, CSP). The later part of this from about 50-75
29 ms onwards represents suppression of motor cortical output. The duration of the CSP
30 increases with the intensity of stimulation and can reach several hundreds of milliseconds
31 (Haug et al., 1992; Inghilleri et al., 1993). The duration of the CSP can be markedly
32 prolonged by intrathecal application of a GABA_B-agonist, suggesting that the CSP is
33 mediated by the induction of GABA_B-mediated long-lasting inhibitory postsynaptic potentials
34 (IPSPs) (Siebner et al., 1998).
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50 This combination of artificial neural synchronisation plus a long lasting IPSP is the main
51 evidence for the “virtual lesion” effect. Together they prevent the continuation of any ongoing
52 neural activity that might have been of behavioural relevance. However, the depth of
53 inhibition and the extent of synchronisation depends on the intensity of the TMS pulse. Thus,
54 intensities that are at threshold for producing a MEP induce only 2-3 discharges in the initial
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1 burst, and the silent period is absent or very short. Intensities that are below threshold for
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3 generating any MEP can generate activity in the cortex, but this is primarily inhibitory. In the
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5 motor area it can be seen either as a small and short lasting suppression of ongoing EMG
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7 activity, or (more clearly) as suppression of a subsequent MEP evoked by a suprathreshold
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9 pulse (Kujirai et al., 1993).
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12 Such small changes in activity may be insufficient to prevent ongoing processing and are
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14 better thought of as added “noise” rather than a “lesion”. The result of adding such noise
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16 could reduce task performance or increase decision times because neural activity would have
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18 to be sampled for longer in order for optimal discrimination of signal and noise. However,
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20 addition of noise can also have the opposite effects. The phenomenon of stochastic resonance
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22 depends upon addition of an appropriate amount of noise bringing a subthreshold input signal
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24 to threshold: in this case, noise enhances processing.
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30 In practical terms it can be difficult in any one situation to disentangle whether the effect of a
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32 TMS pulse is equivalent to a “virtual lesion” or to addition of “noise”. However, a recent
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34 experiment in the visual system addressed this quite successfully (Harris et al., 2008).
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38 Subjects had to discriminate briefly presented contrast gratings to which various amounts of
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40 visual noise could be added. In addition they could also receive a TMS pulse 100ms after the
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42 presentation of the grating. Addition of either a TMS pulse or visual noise increased subjects’
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44 detection threshold. However, if both were applied in the same trial, the effect of TMS and
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46 visual noise were not additive, they were multiplicative. The implication was that the TMS
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48 pulse was not adding “noise” to the system; the results were best interpreted as a loss of signal
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50 effect caused by TMS.
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58 **State dependency of TMS in the motor cortex**

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1 MEP measurements initially highlighted another fundamental feature of TMS by showing that
2 the state of the stimulated cortex has a marked influence on the effect of TMS. Voluntary pre-
3 contraction of the target muscle is an impressive example how strongly a change in functional
4 state can impact on the brain response that can be elicited with TMS: a magnetic stimulus that
5 is just suprathreshold for evoking a motor response will induce a considerably larger motor
6 response in the target muscle if the subject performs a slight voluntary pre-contraction. It is
7 important to note that these relationships occur because the responses that are measured
8 require activation of synaptic connections. Thus, the number of axons that are stimulated by
9 the TMS pulse probably changes very little with changes in activity. However, spread of
10 excitation along synaptic connections is highly state dependent.
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25 The state of the cortex not only determines the overall neuronal response of the stimulated
26 cortex but also shapes the responsiveness of distinct subpopulations of cortical neurones.
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29 When participants prepare to grasp different objects, transcranial excitability of cortico-
30 cortical inputs to the corticospinal output neurones that project from M1_{HAND} to the muscles
31 that will be used for the grasp was specifically enhanced for at least 600 ms before the
32 grasping movement (Cattaneo et al., 2005). There is also evidence that the excitability of
33 cortical motor representations that do not subserve a specific movement are actively inhibited
34 during movement execution and thus, become less responsive to TMS (Sohn and Hallett,
35 2004; Stinear and Byblow, 2003). Context-dependent changes in the excitability of distinct
36 motor representations within the M1_{HAND} have been demonstrated in many TMS studies on
37 motor control, including passive movements (Lewis et al., 2001), action observation
38 (Gangitano et al., 2001; Strafella and Paus, 2000), and motor imagery (Stinear and Byblow,
39 2003, 2004).
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57 It is tempting to conclude that the relative level of activity in distinct neural populations
58 within the stimulated region determines the responsiveness of these populations to TMS.
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1 Thus, it is often asserted if neuronal populations in the M1_{HAND} are active in a motor task then
2 they will be more readily activated to produce a larger motor response to TMS. Conversely,
3 those sets of neurones that are inactive during a task or even inhibited, will be less excitable
4 and show a context dependent reduction in MEP amplitude. However, careful examination of
5 the examples above shows that it is clearly incorrect to equate *activity* in a population with
6 *excitability* to TMS. For example, in the experiments of Cattaneo (2005) on grasping, TMS
7 responses are facilitated in muscles that are about to be used in a forthcoming grasp, but at the
8 time of the stimulus, those neurones are not actually actively discharging.

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Physiological studies show that as a rough rule, neurones are most excitable when their
membrane potential is just below threshold but not discharging. Conversely, if they discharge
at high rates then the excitability declines. However, the exact relationships depend on a
variety of factors including amplitude of the input versus ongoing noise as well as changes in
membrane resistance as well as membrane potential.

A model of the responsiveness of a single spinal motoneurone explored by Matthews (1999)
illustrates how complex the relation can be (Figure 1a). The simulation shows that a given
excitatory input to a motoneurone produces a steeply rising increase in response probability
when at rest (MN silent), whereas if the motoneurone is already discharging at say 10 Hz,
then small inputs have a greater probability of producing firing than at rest whereas large
inputs are less effective than at rest. In TMS terms the input is equivalent to the synaptic input
evoked by the axons that had been activated by the stimulus (which as noted above we can
assume to be constant since axonal threshold is not much affected by the mean level of
ongoing activity). The output is cell discharge which can potentially cause the “virtual lesion”
or added “noise” effect. The graph implies that if all other factors are controlled, the effect of
small TMS pulses might be facilitated if the cortex is active, whereas the response to a higher
intensity pulse might be suppressed relative to rest.

1 The size of the input in relation to ongoing synaptic activity is also important (see Figure 1b).
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3 Thus for any level of activity in the cortex, the synaptic input could be relatively constant (i.e.
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5 low noise) or it could fluctuate a great deal (high noise). The motoneurone model shows that
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7 the probability that a given input (i.e. a TMS pulse) will activate neurones is much reduced
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9 during periods of high noise (twofold synaptic noise). Given that BOLD contrast imaging is
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11 very sensitive to levels of synaptic activity this would lead to the paradoxical conclusion that
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13 areas appearing to have a highly active BOLD response during a particular task might actually
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15 be less responsive to TMS inputs. The conclusion is that although state-dependency of TMS
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17 responses clearly occurs, the interpretation of the effects and generation of rules about what
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19 might happen in other conditions is very difficult.
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28 **State dependency of TMS effects in the visual cortex**

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31 The state dependency of TMS-induced functional effects has also been demonstrated in the
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33 visual cortex by measuring the threshold for inducing illusory visual percepts (phosphenes)
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35 with occipital TMS (Bestmann et al., 2007a; Romei et al., 2008; Silvanto et al., 2007). The
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37 moment to moment expression of alpha activity in the occipital EEG positively correlated
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39 with the phosphene threshold (Romei et al., 2008). It is tempting to say that alpha power
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41 indicates that the occipital cortex is in an idling state, and therefore that this state is less
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43 excitable by TMS. Although correct, this is no more than a restatement of the results and not a
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45 causal explanation. In fact, rather than being idle, the presence of high levels of alpha indicate
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47 that quite a lot of synaptic activity is going on. The important thing is that compared with
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49 periods of low alpha, the activity is more synchronised when alpha levels are high. So why
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51 are phosphenes more difficult to evoke during periods of high alpha activity? One possibility
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53 is that during periods of high alpha, the TMS pulse can only activate neurones on one
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55 (depolarised) half of each cycle, whereas there would be a much higher probability of
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1 activation if there were smaller swings in synaptic potential. However, this is speculation; the
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3 model above warns us that intuition is not to be relied on in such conditions. For example, a
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5 completely different explanation could be that the actual response to TMS is the same in all
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7 states, but that perceptual discrimination is more difficult during periods of synchronised
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9 (high alpha) activity.
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12 In another study, colour adaptation was used as an experimental manipulation to induce an
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14 imbalance in the activity of distinct neuronal populations within the same visual areas
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16 (Silvanto et al., 2007) . In a first experiment, subjects adapted to a uniformly coloured
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18 stimulus which produced a visual after image of the complementary colours in the same
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20 spatial arrangement as the adapting stimulus. During this state of imbalance with increased
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22 activity of neuronal representations that are the colour of the after image and reduced activity
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24 of neuronal representations of the colour of the adapting stimulus, single-pulse TMS was
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26 applied at 110% of individual phosphene threshold. In this state of functional imbalance,
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28 TMS-induced phosphenes, which are usually colourless, assumed the colour to which subjects
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30 were adapted “as if a region of the visual afterimage had been replaced with the colour of the
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32 adapting stimulus”(Silvanto et al., 2007) . Similar results were obtained in a task in which
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34 participants had to detect the colour of briefly presented gratings that were either congruent
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36 with the adapting stimulus (i.e. same colour and orientation), incongruent (i.e. opposite colour
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38 and orientation) or partly congruent (shared either colour or orientation) after adapting to a
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40 conjunction of orientation and colour. Three pulses of TMS were given to the visual cortex 0,
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42 50, and 100 ms after target onset. In the control condition, visual adaptation enhanced the
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44 detection of stimuli incongruent with the adapting stimulus and depressed detection of fully
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46 congruent stimuli. Application of TMS cancelled the adaptation-induced difference in
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48 detection performance between the fully incongruent stimuli and fully congruent stimuli.
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1 Based on these results it was argued that the neurodisruptive effects of TMS have a relatively
2 greater impact on less active neurones, akin to microstimulation of the less active neural
3 populations (Silvanto et al., 2007) . At first sight this might seem a little counterintuitive if we
4 go back to the original assumption that *activity equals excitability*. In this case, the less active,
5 adapted neurones should be less excitable. However, as we can see from the model above this
6 is not necessarily the case.
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14 To understand this it is important to go back to the experiment. When subjects stare at, say, a
15 red pattern, the red photoreceptors of the retina become fatigued and less sensitive to red light.
16 Thus, when subjects then look at a white background, the red receptors are less active than the
17 blue and green ones and the subject sees cyan where s/he had previously seen red. Presumably
18 at the cortex, this means that neurones responsive to red inputs will receive less than normal
19 red input, and hence they discharge fewer impulses in comparison with the blue and green
20 sensitive neurones. In this state, it is possible that they are more readily activated by a TMS
21 pulse than the more rapidly discharging blue and green neurones. Thus, in the first experiment
22 with phosphenes, the percept evoked will be “redder” than usual.
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38 It is more difficult to analyse what may have happened in the second experiment. Although
39 there may have been some adaptation of retinal red receptors, the fact that the effect was
40 selective for both orientation and colour of the grating suggests that it involves cortical rather
41 than retinal adaptation. Without any TMS, prolonged viewing of a red, 45 degree angle
42 grating might cause adaptation of a set of colour/orientation selective neurones in visual
43 cortex. This would reduce subsequent detection of a grating with the same orientation and
44 colour. If there existed some antagonistic interaction between orientation/colour selective
45 neurones then we might also expect the observed increase in detection of gratings of the
46 opposite orientation and complementary colour.
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1 The authors speculate that adaptation to a 45 degree/red grating increases the sensitivity of the
2 orientation/colour neurones in the cortex to TMS. Thus in trials where TMS is given, the 45
3 degree/red neurones are activated more than other orientation/colour neurones. This brings
4 their sensitivity to visual inputs back to baseline, and detection of 45 degree/red grating is
5 increased. It would also provide a competing activity that would make detection of the
6 incongruent colour/orientation similar to that seen at baseline. As we have seen in the model
7 motoneurone it is certainly possible that reducing the activity of a neurone can increase the
8 chance that it will discharge in response to a TMS pulse. This extra activity could then add on
9 to the activity evoked by a 45 degree/red grating and increase the chances of detection; it
10 might also interfere with detection of gratings of opposite orientation and colour.
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25 However, as always with TMS experiments, there is an opposite explanation. An important
26 feature of both experiments was that TMS was given during an illusory visual percept (the
27 presence of a coloured afterimage). In this state, the functional effect of TMS could be
28 primarily inhibitory. If so, TMS should induce a stronger suppression of activity in the more
29 active neuronal presentations coding the colour of the afterimage and spare the inactive
30 neuronal presentations coding the colour of the adapting stimulus. This might flip the
31 functional imbalance in neuronal activity between the complementary neuronal
32 representations and induce an illusory percept of the adapting stimulus (experiment1) and
33 cancel the adaptation-induced difference in detection performance (experiment 2). This
34 scenario is not far-fetched as extracellular single-unit recordings in cat visual cortex revealed
35 distinct episodes during which spontaneous and visually evoked activity were enhanced and
36 suppressed by a single biphasic TMS pulse (Moliadze et al., 2003). Critically, strong biphasic
37 stimuli exceeding 50% of maximal stimulator output led to an early suppression of neuronal
38 activity during the first 100-200 ms, followed by stronger (rebound) facilitation, showing that
39 under some conditions, inhibitory effects may prevail after TMS of the occipital cortex.
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State dependency and spread of excitation to connected brain regions

The notion of state dependency not only applies to the regional neuronal response to TMS at the site of stimulation but can readily be extended to the transsynaptic spread of excitation to connected brain areas. The cortico-cortical interactions that can be probed with bifocal TMS of two connected areas show dynamic changes during an experimental task (Koch et al., 2006; 2007; Murase et al., 2004). For instance, the ipsilateral facilitatory interaction between right posterior parietal cortex and M1_{HAND} was only present at two specific time points (50 and 125 ms after an auditory cue) during the reaction time of a reach task and only when a leftward reach was planned, showing that the parieto-motor connectivity is enhanced during early stages of planning a reach in the contralateral direction (Koch et al., 2008).

The state dependency of TMS-induced spread of excitation to connected cortical areas has been further corroborated in studies that combined TMS with functional brain mapping. A combined TMS-EEG study showed a break-down of the TMS-induced spread of activation to connected cortical areas during slow-wave sleep relative to wakefulness (Massimini et al., 2005). A recent study interleaved TMS with fMRI to show that TMS to left PMd influenced activity in contralateral right PMd and M1_{HAND} in a state-dependent fashion (Bestmann et al., 2007b). Compared to low-intensity TMS, high-intensity TMS led to activity increases in contralateral right PMd and M1 during a left-hand gripping task. In contrast, high-intensity TMS decreased activity in these areas relative to the low-intensity TMS condition when subjects performed no grip. There was also stronger interhemispheric coupling between left and right PMd, when high-intensity TMS was applied to left PMd during left-hand grip.

The state-dependent changes of TMS-induced effects on functional connectivity between the stimulated and remote areas parallel those on regional activity in the stimulated cortex showing a stronger impact of TMS on active cortico-cortical connections. This implies that

1 neuronal excitation spreads more efficiently throughout a neuronal network if the connections
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3 are in an activated state, presumably producing a stronger disruptive effect on the functional
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5 interplay between the stimulated area and connected brain regions.
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10 **A neurophysiological framework of TMS-induced neurodisruption**

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12 A TMS pulse to the cortex produces a synchronous burst of activity in a proportion of
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14 available neurones. This is followed by a longer lasting IPSP, which together with the burst
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16 will interfere with any processing that the cortex was doing at the time of the stimulus
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18 (“virtual lesion”). The size of the neural population that is affected will depend on the
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20 stimulus intensity and the intrinsic excitability of the neurones.
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26 A TMS pulse of constant size does not always have the same effect. The response changes
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28 according to the state of the cortex when the stimulus is applied (state dependency). This is
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30 because the state affects the distribution of excitability in the population of neurones. It is
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32 important to remember that the cortical state is unlikely to alter the number of axons that are
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34 activated by the TMS pulse. Rather it affects the transmission of impulses across synapses
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36 innervated by these axons. We wish to stress that it is very difficult if not impossible to
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38 produce a simple set of rules that will explain how the effect of TMS depends on state. This is
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40 because there is no simple relationship between the *excitability* of a region and the *activity* in
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42 that region. Thus, interpretation of state dependent effects is always speculative.
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32 33 34 35 36 37 **Figure Legend**

38 39 **Figure 1. Model of the responsiveness of a single spinal motoneurone to a synaptic input**

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42 In **panel a**, the abscissa shows the conductance change of a stimulus with increased excitatory
43 conductance. The ordinate gives the response of the unit; it shows the number of extra spikes,
44 above the resting level, produced by the stimulus and is expressed as the percentage
45 probability of the unit responding to the stimulus (i.e. the increase in its 'firing index'). MN=
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Panel b depicts the variation of the response size depending on a twofold change in synaptic noise. The abscissa plots the background excitatory conductance. The occurrence of a

1 maximum depends upon the size of the stimulus relative to the noise rather than upon its
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3 absolute magnitude (adapted from Matthews (1999)).
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Figure 1a
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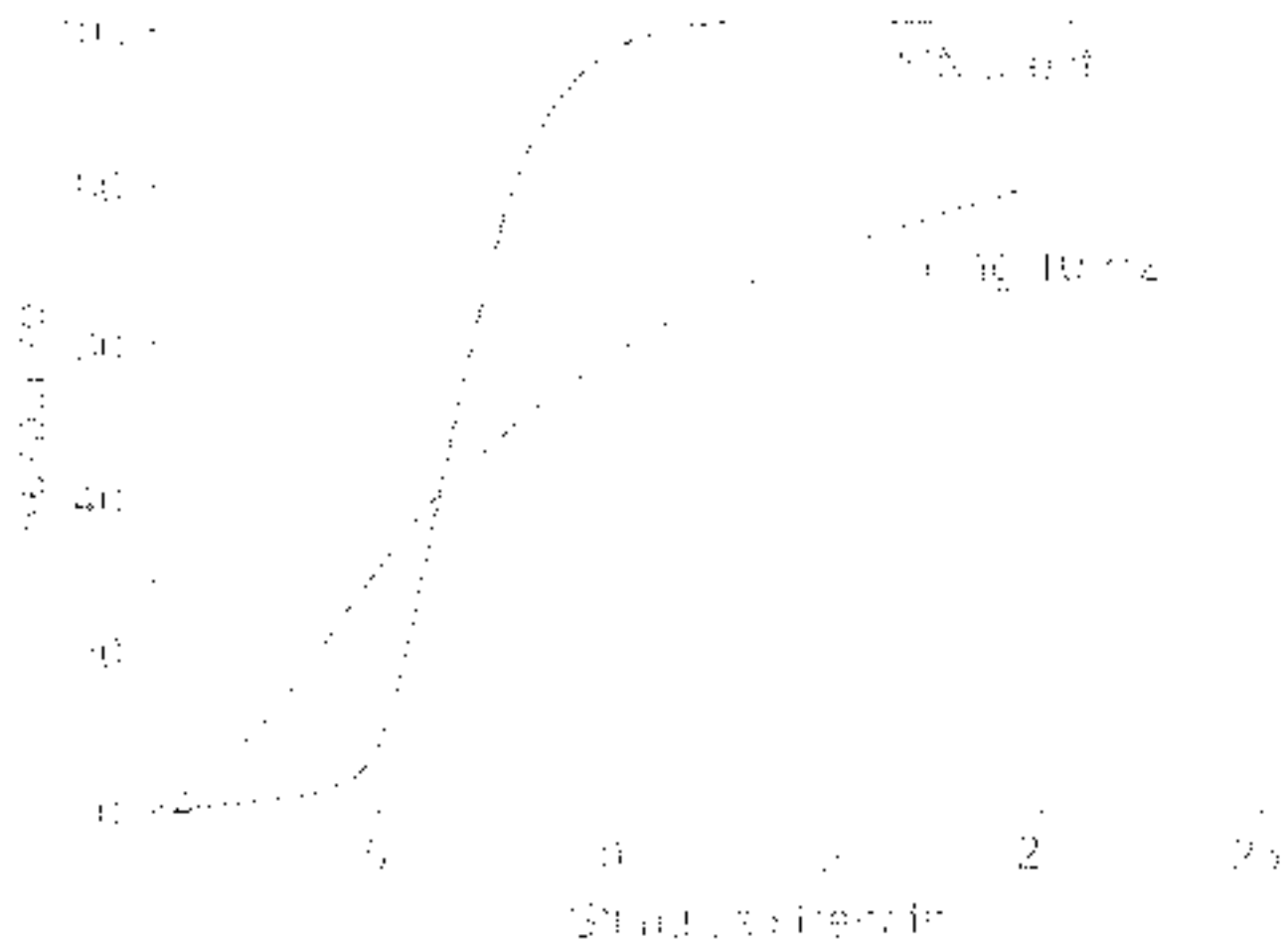


Figure 1b
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