Practical Issues in Treatment Provision

6

6.1 Introduction

At the commencement of a treatment course, the prescribing practitioner is required to determine a variety of parameters for treatment provision. The choice of these should be made on an individual patient basis but may be influenced or largely determined by local policies or established protocols. Each of the following parameters must be explicitly prescribed for each patient or made clear in local protocols:

- Intensity of stimulation
- Frequency of stimulation
- Duration of each stimulation train
- Total number of stimulation trains provided in each treatment session
- Inter-train interval
- Site of stimulation
- Coil orientation

6.2 Dosing and Motor Threshold

The intensity of stimulation provided during rTMS treatment is typically defined as a percentage (usually between zero and 100 %) of the total machine output provided by the rTMS device being used. The intensity for each patient is individualised; it is typically determined relative to that individual's resting motor threshold (RMT). The RMT is an estimate of an individual's level of motor cortical excitability, established by the application of single TMS pulses to the motor cortex. The lowest stimulation intensity required to consistently induce a motor response in a peripheral muscle is determined, usually in the abductor pollicis brevis (APB) in the contralateral hand. This sets the RMT (see Boxes 6.1 and 6.2).

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Box 6.1. Assessment of the Resting Motor Threshold (RMT): Theory

Typically, the RMT is defined as the minimum machine stimulator intensity required to produce a pre-specified motor response. Most commonly, this is a defined number of motor twitches observed on a certain number of occasions (e.g. on 3 out of 5 or 5 out of 10 stimulations).

The RMT is determined by a number of factors. These include intransient factors such as the distance between the stimulation coil in the cortex and variable factors such as medication status and sleep deprivation. Critically, the resting motor threshold is also sensitively dependent on the absence of any muscle activity. If the patient has a background level of motor activity during measurement, the RMT measured is likely to be considerably lower than the true value.

The type of motor response can be assessed in one of two ways:

1. The visual observation of a muscle twitch in the contralateral hand from the site of stimulation.
2. The measurement of a motor evoked response of a specific size in the contralateral hand. This is achieved using electromyographic equipment (EMG): a significant motor response is usually defined as an EMG deviation (motor evoked potential) of greater than 50 uV peak to peak.

Assessment of the RMT with visual observation is simple and does not require the knowledge needed to set up EMG monitoring. However, EMG monitoring does give reassurance that the patient is maintaining an adequate level of muscle relaxation. In the absence of this, considerable effort should be given to ensure the patient is as relaxed as possible throughout assessment of the RMT.

It is likely that assessment based on EMG or visual observation methods generate a similar figure within individuals although studies investigating this are not completely consistent [1, 2]. The EMG is capable of detecting non-visible motor twitches but will only detect activity in a single muscle. This increase in sensitivity is typically balanced by the fact that when visualising muscle activity, it can be considered in one of a number of muscles. If RMT is measured in this way, it is likely to be of similar sensitivity to the EMG method.

The RMT can potentially be quantified in several ways. As described above, one approach is to define the RMT as a minimal intensity at which a certain number of motor evoked responses are invited out of a predetermined number of pulses: for example, the minimal intensity of which five motor responses are seen during ten stimulation pulses. However, more recently, several software algorithms have been developed that estimate the RMT from the size and presence of motor responses at varied stimulation intensities (e.g. as used in [3] and [4]), although there remains some debate about the relative advantages and disadvantages of some of these [5]. Variation in the method for measurement of RMT does further complicate the comparison of outcomes of various clinical trials. However, improvement in RMT estimation methods is likely to restrict the variability of measurements recorded rather than result in a systematically higher or lower threshold used for stimulation.

It is notable that the RMT is a measure of motor cortical excitability, not a measure of excitability of the prefrontal cortex where depression treatment is

typically applied. Methods to quantify thresholds in prefrontal regions have yet to be developed. The use of the RMT as an estimate for prefrontal treatment has support from the clinical trials of rTMS depression treatment in which few safety concerns, including only minimal incidences of seizure induction, have arisen.

Box 6.2. Assessment of Resting Motor Threshold (RMT): Techniques

A number of methods have been described for the estimation of the RMT. The basic procedure is presented here for measurement of the RMT and quantification using a simple counting method.

1. Place the coil with its centre approximately 2 cm lateral and 5 cm anterior in a parasagittal plane from the vertex. This will be approximately in line with the ears.
2. Position the coil to be on an approximately 45° angle from the midline (see Fig. 6.1).
3. Place your other hand gently yet firmly on the other side of the subject's head. Take care not to press too hard with that hand, or to press down too firmly on the coil.
4. Beginning with the intensity low (30–35 %), commence single-pulse stimulation with pulses every 3–5 s. Slowly move the coil around the estimated location of the motor cortex, applying one or two pulses at each site.
5. If no movement/twitch is observed in the contralateral hand, then the RMT for that person is higher than the current TMS output setting. Therefore, increase the output in steps of 5 %, testing the response at a number of sites at each step.
6. If a hand and/or wrist movement is observed, then the applied intensity is close to RMT. Test responses at a number of areas and mark the site on the scalp which appears to produce the greatest motor response.
7. With the intensity set at a level that produces a small but regular muscle twitch, establish the scalp location that produces the optimal response. To do this, test the response to two or three pulses over an imaginary grid of points surrounding the site which you have marked (see Fig. 6.2). Mark the optimal location.
8. Providing stimulation with pulses of approximately 0.2 Hz at the optimal location (no more frequent than one pulse every 5 s), now establish the motor threshold by your chosen method (algorithm or counting). Note, if higher frequencies of stimulation are used, this may in itself affect cortical excitability confounding RMT assessment.
9. If using a counting method, apply pulses at a slightly suprathreshold intensity: if three muscle movements are observed during five pulses (or 5 out of 10), consider this level above threshold and reduce the intensity by 1 %. Repeat this procedure until 3 (or 5) responses are not seen. The RMT is 1 % higher than this level. The same procedure can be undertaken with EMG where a 50-uV motor evoked potential response is considered above threshold.

Note: You may often see a thumb movement/twitch from the very first pulse at any given intensity level but then no observed movement following further stimulation: the response is typically greater to a first rather than subsequent pulse. A failure to get consistent responses indicates that you are below RMT.

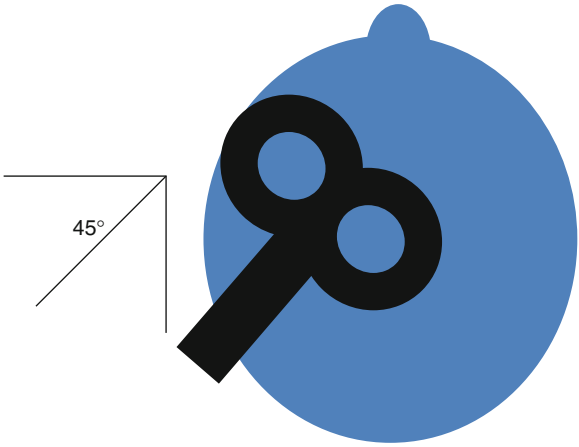

Fig. 6.1 Coil orientation at 45° to parasagittal plane

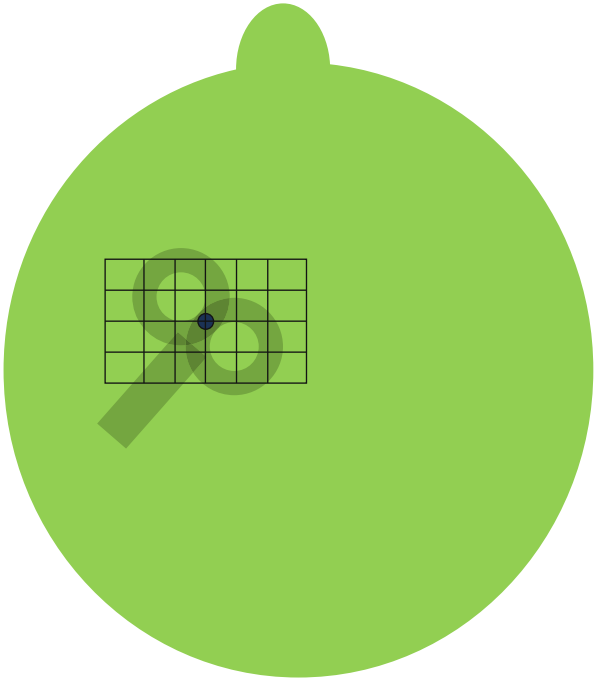

Fig. 6.2 Grid of sites: in the localisation of the optimal site for motor cortical stimulation, a series of points around the estimated optimal site should be systematically stimulated at a fixed intensity to establish the optimal site of stimulation

Across time there has been considerable variation in stimulation intensity used within rTMS treatment trials for patients with depression. Initially, trials used intensities below the RMT (80–90 %). However, in more recent years, trials have more typically used suprathreshold intensities of 110–120 %. The intensity used for stimulation has implications potentially for efficacy and definitively for safety and tolerability. In regard to efficacy, it has been proposed that the progressive increase in stimulation intensity in treatment trials over time may have contributed to greater treatment effects in more recent studies [6]. However, a substantial number of other factors have also changed over time, including the duration of treatment courses, and little direct data has evaluated the relative efficacy of treatment based on intensity relative to RMT. Higher intensities do have significant implications for safety and tolerability. Patient discomfort and pain during treatment, and the development of posttreatment headache, are certainly more common at higher treatment intensities. In addition, higher intensities are related to a greater risk of seizure induction. The risk of seizure induction is dependent on stimulation intensity, the duration of stimulation trains and the inter-train interval. According to established safety guidelines, when rTMS is applied in high-frequency trains, stimulation can safely be applied up to 120 % of the RMT if the stimulation train duration is limited to 4.2 s [7]. Little research has explored the safety implications of the interval between trains: with 10 Hz trains, some authors have proposed that the interval should be at least twice the duration of the actual train itself. At lower frequencies, the train can be extended safely to longer durations (see Table 7.1). Note, however, that the safety guidelines have only been established for stimulation in the motor cortex: no equivalent data has been obtained in regard to safety for stimulation in frontal areas used in depression treatment.

Although a specific frequency may be prescribed for a course of treatment, local practice may determine that the intensity be varied depending on factors such as patient tolerability. This may be done in one of two ways: first, the prescribed treatment intensity can be applied and the intensity lowered if this is not tolerated by the patient. Second, the patient may be commenced at a lower treatment intensity which is then progressively increased depending on tolerability. In our experience, the latter approach is preferable. If patients experience significant pain at an initial high intensity, they are more likely to be dissuaded from continuing treatment or be hypervigilant during subsequent treatment trains. Hypervigilance may increase scalp muscle contraction, further increasing the unpleasant experience of treatment. In contrast, if a positive experience of treatment is established on a low treatment intensity, intensity may be gradually increased to levels that may not otherwise have been well tolerated. Some idea of the individual patient's tolerance to treatment may be estimated during measurement of the RMT. In more sensitive patients, we would recommend commencing treatment between 40 and 50 % of the RMT and progressively increasing depending on tolerability. Although it would seem desirable to achieve maximal prescribed intensities (e.g. 120 % of the RMT), brain effects of rTMS are clearly apparent at much lower levels (e.g. 90 % of the RMT). It may be preferable to have a patient receive a treatment course at a lower intensity than to drop out of treatment altogether due to lack of tolerability of high-intensity stimulation.

This is certainly the case given that the existing clinical data does not strongly suggest a linear relationship between stimulation dose and efficacy.

As indicated previously, the RMT can be influenced by a number of patient specific factors such as medication status. Medications that suppress cortical excitability, such as benzodiazepines, are likely to increase the RMT. Importantly, withdrawal of benzodiazepines, or withdrawal of other CNS depressant medications such as alcohol, is likely to increase cortical excitability and substantially lower the RMT. If patients change CNS active medications or drug use during a course of treatment, the RMT should be reassessed and the intensity of stimulation adjusted if it is considered safe to continue with treatment.

There is also individual variation in the RMT across hemispheres. Although one study found no significant group average differences between left and right RMT in depressed patients [8], for individual patients, RMT levels can vary by up to 10 % across hemispheres. Therefore, measurement of the RMT in the hemisphere in which treatment stimulation is to be provided is recommended.

It is also possible that the RMT varies significantly across time even in the absence of changes in external factors such as medication dose. A small number of patients in a 2-week trial of rTMS experienced a significant shift in RMT level that could justify recalibration of treatment dose, although no significant group variation was found [8]. A decision to remeasure RMT over time should be influenced by considerations as to whether the patient is close to safety thresholds in the baseline dose applied. The baseline RMT level does not appear to influence the outcome of treatment [9].

Note: The intensity of stimulation will vary substantially between different brands of rTMS equipment and between different TMS coil types. It is also possible that it will vary significantly when the same machine but different coils are being used. If an individual patient is to be treated with more than one device or coil, it should be established prior to treatment if there is any variation. The easiest way to do this is to measure the resting motor threshold with the different device/coils on several patients to establish the consistency of the measures obtained.

6.2.1 Clinical Recommendations

Although there are limitations in the applicability of RMT measures to prefrontal areas, at this stage, rTMS dosing should be based on individual measurement of the RMT. There are a variety of methods for RMT assessment, a number of which are likely to be equivalent in practical implementation. The most important consideration is that each prescribing clinician is trained in and familiar with the method that he or she is able to apply consistently. RMT should be assessed at the start of each acute course of treatment to determine dosing based on safety and efficacy considerations in the hemisphere to which stimulation will be applied. The RMT should be reassessed when patients alter their consumption of CNS active drugs. The RMT should also be periodically reassessed when patients have extended treatment courses or maintenance rTMS over time.

6.3 Selection of Treatment Type and Parameters

As discussed in Chapter 4, a considerable body of research has evaluated a variety of methods of rTMS application including high-frequency stimulation applied to the left DLPFC, low-frequency stimulation applied to the right DLPFC and variations of bilateral stimulation. Clearly, the vast majority of research has established the efficacy of high-frequency stimulation applied to the left DLPFC, most commonly at 10 Hz. This data includes the pivotal Neuronetics Ltd-sponsored clinical trial that led to device registration in the USA. As such, it is likely that high-frequency stimulation applied to the left DLPFC is likely to be the initial rTMS treatment option selected for most patients.

6.3.1 Considerations with Left-Sided High-Frequency rTMS

6.3.1.1 Frequency

Although there are antidepressant studies of the effect of frequencies such as 5 and 20 Hz, the vast majority of studies have been conducted with 10 Hz stimulation. This includes the two main large randomised multisite rTMS trials [3, 10]. There are no studies showing any particular advantage of stimulation at other frequencies. Given the depth of research that has focused on this particular frequency, unless evidence emerges to the contrary, most treatment should be provided at 10 Hz.

6.3.1.2 Train Duration and Intensity

As discussed previously, there is a relationship between train duration and intensity in regard to the safety of rTMS administration. If trains are to be provided at an intensity of 120 % of the RMT, train duration should be limited to 4.2 s. Longer trains, most commonly 5 s in duration, can be safely administered at lower intensity, for example, 110 % of the RMT.

6.3.1.3 Train Number

Seventy-five trains of 10 Hz stimulation were applied in the two large multisite rTMS trials conducted to date [3, 10]. This was considerably in excess of the number of trains used in most trials until that time, with previous studies often applying only 20–30 trains. Given that the remission rates in both of these trials were fairly modest, it is not clear whether this increase in train number resulted in substantially greater efficacy than had been seen previously. Specific research is urgently required to determine whether there is a direct relationship between treatment dose (pulse number) and clinical response. In the absence of this data, the provision of 75 trains per treatment session is becoming a de facto standard treatment approach.

6.3.2 Use of Right-Sided Low-Frequency rTMS

There are a number of potential advantages of low-frequency right-sided rTMS that could lead to its potential consideration as first-line treatment or alternatively as an approach in circumstances where high-frequency stimulation cannot be tolerated or may be considered potentially unsafe. Low-frequency stimulation, especially as it is known to reduce cortical excitability rather than increase cortical excitability, is likely to be associated with a substantially lowered risk of seizure induction. Therefore, there may be circumstances in which the risks associated with a trial of low-frequency stimulation may be considered appropriate where high-frequency stimulation raises too high a risk of seizure induction. This could be because an individual patient has a risk factor for seizure induction or heightened cortical excitability. It could also be because the risk of actually experiencing a seizure may be considered too high, for example, in somebody with compromised cardiac function. It should be noted, however, that the risk of seizure induction with low-frequency stimulation is not zero but is likely to be less than with high-frequency stimulation.

Another circumstance in which low-frequency right-sided stimulation may be considered as an alternative is where high-frequency stimulation is not tolerated by individual subjects. The vast majority of patients will find low-frequency stimulation more tolerable than the intense bursts of high-frequency stimulation although this is not universal.

Finally, right-sided stimulation may be considered as a treatment option in patients who have failed to respond to high-frequency left-sided rTMS. Studies which have compared the two approaches have generally found equivalent efficacy. Little research has explored rates of response to one treatment in the event of failure of the other. We previously found that a minority of patients will respond to a trial of high-frequency left-sided rTMS if they had failed to respond to low-frequency right-sided rTMS. However, no systematic research has explored crossover in the opposite direction. However, given the low risks associated with right-sided low-frequency stimulation, this could be considered a treatment alternative in some patients.

6.3.2.1 Dosing of Right-Sided Low-Frequency rTMS

Early studies of right-sided low-frequency rTMS applied a small number of 60 s trains, usually with a 30 or 60 s inter-train interval. More recent studies have commonly used a single 15 min train (900 pulses) in each treatment session. This dosing remains much lower than the common dosing with 10 Hz stimulation (3,750 pulses across 75 trains per session), but no studies have explored higher low-frequency doses. Based on the existing data, a single 15 min treatment session at 120 % of the RMT appears a conservative and sensible approach.

6.3.3 Sequential Bilateral rTMS

At this time, it is not clear whether bilateral rTMS has a role in clinical practice. Although some studies of sequential bilateral rTMS were promising [11] and at

least one study has found superior efficacy than unilateral treatment [12], a number of studies have found equivalent or inferior responses to bilateral compared to unilateral rTMS (e.g. [13]). Based on this research, there are no clear indications for bilateral rTMS at this time.

6.3.3.1 Clinical Recommendations

At this stage, under most circumstances, first-line rTMS treatment is likely to entail 10 Hz stimulation applied to the left DLPFC. Under most circumstances, a dose of 75 four second trains applied at up 120 % of the RMT is recommended. It is likely that many patients, especially those with a RMT of greater than 50 %, will benefit from a progressive increase in treatment intensity over the course of one or more treatment sessions until the target dose is achieved. When practitioners measuring the RMT have limited experience, dosing at 110 % of the RMT is sensible to ensure that there is a margin of safety in case of minor errors in RMT estimation. Low-frequency right-sided stimulation is a good option for patients who have trouble tolerating left-sided treatment, who have additional risk factors for seizure induction or when left-sided treatment has failed to produce therapeutic effects.

6.4 Treatment Scheduling and Duration

The vast majority of rTMS studies have provided treatment 5 days per week, Monday to Friday. Two studies have explored whether this frequency of treatment is required for adequate efficacy. In the first study, one group of patients received treatment 5 days a week for 2 weeks, and the second received three treatments in week 1 and two treatments in week 2 [14]. No significant differences between the groups were seen in outcomes although the sample size in this study was relatively small. In a more recent study, 77 patients were randomised to receive either rTMS 5 days a week for 4 weeks (20 treatments) or treatment 3 days a week for 6 weeks (18 treatments) [15]. When assessed at 4 weeks, the patients who received daily treatment had improved to a greater degree. However, similar efficacy was achieved by the two groups when end-of-treatment assessments were compared. This indicated that more widely spaced treatment resulted in a slower response, but a response of a similar degree of efficacy. We have some limited experience in the provision of treatment 7 days per week. The patients treated in this way mostly have not been noted to respond more quickly and on several occasions have actually required further treatment sessions such that the overall treatment duration remained approximately 4 weeks. Limited research has explored the use of twice-daily rTMS [16]. Although this appears as effective, we lack studies comparing twice daily to once daily rTMS. Overall effect sizes seen do not seem to be greater than that seen with standard treatment.

Trials to date have varied considerably in how they have dealt with missed treatment sessions or extended session breaks, for example, over long weekends. In our experience, treatment can successfully proceed when patients have missed individual treatment sessions, but it would seem sensible to try and provide at least three treatment sessions within each week period and to limit protracted breaks.

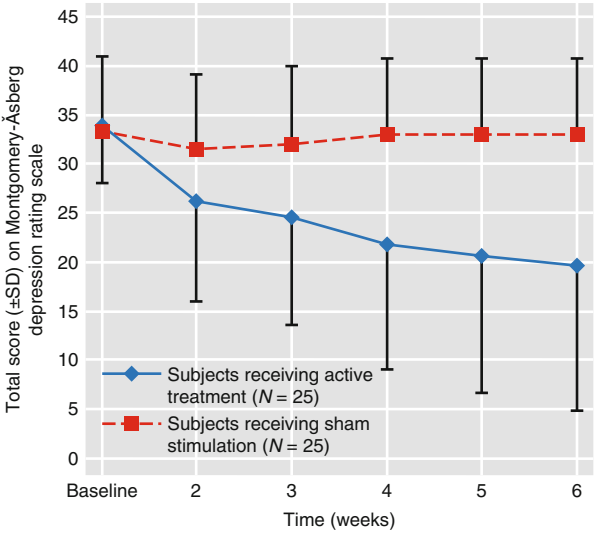

Fig. 6.3 The progressive reduction in depression scores in a clinical trial of bilateral rTMS seen in active treatment group over a 6-week period [11]

In regard to the duration of rTMS treatment courses, these have varied across time from 1 week in initial studies to 6 weeks or longer in studies published in recent years. One method of analysis has suggested that better clinical responses have been seen in more recent clinical trials than earlier studies; it is possible that the increasing duration of treatment is a factor in this improvement [6]. There does appear to be a progressive improvement in mood across time during treatment implying that longer courses of treatment are likely to result in better clinical outcomes. For example, there was a clear reduction, week by week, in depression severity across a 6-week period of time in the active treatment group in a trial of sequential bilateral rTMS conducted by our group (see Fig. 6.3) [11].

It is not clear, however, whether there is an optimal period of treatment. In a series of open-label clinical trials we have conducted, substantial response and remission rates have been achieved with 4 weeks of treatment. However, a subpopulation of patients does require a longer period of treatment to achieve substantial response. Although most patients will initially report some improvement during either week 2 or week 3 of treatment, occasionally patients do not experience mood shifts until considerably later. Four weeks seem to be a reasonably balanced minimal duration of adequate treatment. Unless patients have previously responded to a course of rTMS, we would rarely recommend continuing beyond 4 weeks if no clinical improvement has been achieved to date. A trial of right-sided treatment or another type of non-rTMS therapy should be considered under those circumstances. However, when patients have achieved partial response by the 4-week time point, extending treatment beyond this is clearly warranted and justifiable.

It can also be unclear when to cease treatment when a patient has responded clinically. Generally, patients should continue treatment whilst they are improving, but once clinical response has reached a plateau at an adequate level, we typically

recommend cessation of treatment. However, we frequently also recommend several more treatment sessions to potentially consolidate the gains achieved. It is notable that patients may continue to demonstrate some further improvement after the cessation of treatment, although it is unclear whether this is a neural/brain or psychosocial effect.

There is no evidence of the accumulation of adverse events or side effects with the extension of a course of treatment beyond 4 weeks. Patients tolerating a course of treatment will usually continue to do so. However, limited research has explored the overall safety of longer courses of rTMS treatment.

6.4.1 Clinical Recommendations

rTMS treatment should typically be provided five times per week to achieve efficacy at least equivalent to that seen in clinical trials. However, patients should not be excluded from treatment if they have missed treatment sessions: treatment at slightly reduced frequency, for example, three or four times per week, may be more acceptable to some patients and still maintain reasonable clinical results. Treatment at greater frequency, for example, twice daily or 7 days per week, cannot be justified at this stage.

A minimum duration of adequate treatment with rTMS provided on a daily basis would be 4 weeks, although some patients may require a longer course of treatment to respond. Extension of treatment beyond 4 weeks is clearly justifiable when patients have previously responded to rTMS or have had a partial improvement but continue to experience symptoms after 4 weeks.

6.5 Concurrent Treatments

There are two potential issues with the consideration of concurrent medication treatment: whether there is a possibility of an impact on treatment efficacy, either favourable or not, and whether concurrent medication treatment increases the risk of adverse events such as seizure induction.

In regard to efficacy, a large number of clinical trials of rTMS in depression have included patients receiving antidepressant and often other forms of psychotropic medication. Several of the larger multisite trials (e.g. [3]), however, have been conducted in medication-free patients. When patients on medication have been enrolled in trials, it has been common to include only those who have failed to adequately respond to medication and where the dose of medication has been unchanged for a significant period of time prior to rTMS treatment, often 4 weeks. From the results of these trials, it appears that rTMS is effective in both medication-free and concurrently medicated patients.

The situation is not as clear, however, when we consider the concurrent *commencement* of medication and rTMS treatment. Trials investigating this approach have generally found little difference between active and sham treatment, perhaps

because the possible effects are more limited when concurrent treatment is commenced (e.g. [17]). Concurrently commencing treatment also raises a simple practical clinical issue: if a patient responds under these circumstances, it is not possible to know whether it was the medication, rTMS or the combination, which resulted in clinical improvement. This uncertainty is likely to have implications for future recommendations regarding treatment options if the patient experiences a relapse.

One trial in another disorder did suggest that medication could potentially undermine rTMS response. This early study of the effect of rTMS treatment for auditory hallucinations in patients with schizophrenia found that patients responded more poorly when receiving rTMS concurrent with a mood stabiliser [18]. However, this has not been replicated in other hallucination studies, and analyses in substantial depression samples have not found this effect. In fact, analyses in depression samples have not found a moderating effect of any of the medication classes investigated.

In regard to safety considerations, the main concern is that concurrent medications may alter cortical excitability and contribute to a greater risk of seizure induction (Table 6.1). However, if medication is present at the time of the measurement of the RMT and the dose does not change over time, the effect on cortical excitability is likely to be at least partially controlled for in this initial measurement. However, changes in medication dose during treatment may result in an uncontrolled alteration of excitability increasing risk. Therefore, if substantial changes in medication doses are made, RMT levels should be remeasured and the prescribed rTMS intensity adjusted accordingly.

Of note, the greatest concerns in regard to safety of medication during rTMS treatment are likely to arise with medications known to predispose to seizures or alter excitability. Caution is warranted with clozapine, bupropion, tricyclic antidepressants and stimulants such as amphetamine derivatives. However, a number of studies have included clozapine-treated patients in trials without complication, and we have treated depressed patients concurrently taking medication from all antidepressant classes. We have also treated without incident a number of patients receiving stimulants. However, given the short duration of action of many of the medications in this class, we will often treat at a time of trough plasma levels. We also typically ensure that the measurement of the RMT and the provision of treatment occur at approximately the same time following medication dosing, for example, between 4 and 5 h after the morning or most recent dose.

6.5.1 Clinical Recommendations

There do not appear to be any adverse implications for the commencement of rTMS treatment in patients who are receiving a stable dose of psychotropic medication. Patients who have experienced a partial response to medication should not be weaned off this medication to undergo rTMS treatment unless for other specific reasons. There is no sensible rationale for the concurrent commencement of rTMS treatment and antidepressant medication, and this should be avoided. Careful monitoring

Table 6.1 Seizure risk associated with psychotropic medications

	Drug class	Drug name	Risk	Notes
Antidepressants	Tricyclic antidepressants (TCA)	Imipramine	Majority of TCA medications pose low risk at therapeutic doses	Risk may be higher in genetic slow metabolisers, significantly increased risk at high dose/in overdose
		Amitriptyline		
		Desipramine		
		Nortriptyline		
		Dothiepin		
		Clomipramine	Higher risk	
	Tetracyclic antidepressants	Maprotiline	Higher risk	
		Amoxapine		
	Selective serotonin reuptake inhibitors (SSRIs)	All in class	Low risk	SSRIs can produce hyponatremia which can precipitate seizures
	Bupropion		Risk appears low to moderate in divided doses that total <400mg/day and in slow release form	
	Phenylpiperazines	Trazodone	Low risk	
		Nefazodone		
	Selective serotonin–noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine	Low risk	Possibly higher risk at higher doses
	Mirtazapine		Low risk	
	Monoamine oxidase inhibitors (irreversible)	Phenelzine	Low risk	
		Tranylcypromine		
	Monoamine oxidase inhibitors (reversible)	Moclobemide	Low risk	
	Noradrenaline reuptake inhibitors (NRIs)	Reboxetine	Low risk	

(continued)

Table 6.1 (continued)

	Drug class	Drug name	Risk	Notes
Antipsychotics	Phenothiazines	Chlorpromazine	Higher risk	
	High-potency typical antipsychotics	Haloperidol	Low risk	
	Atypical antipsychotics	Clozapine	Higher risk	Risk is significantly dose dependent
		Olanzapine	Possibly higher risk	
		Quetiapine	Possibly higher risk	
		Risperidone	Low risk	
		Ziprasidone	Low risk	
Mood stabilisers		Lithium	Possibly higher risk	Risk substantially increased at toxic plasma levels
Benzodiazepines		All in class	Low risk	High risk in withdrawal

Data partially summarised from review in [25]

of the RMT and adjustment of treatment dose is required if medication is altered during treatment, especially when patients are receiving medications known to effect cortical excitability or the RMT.

6.6 Coil Positioning and Location

The vast majority of studies that have evaluated the efficacy of rTMS treatment in depression have utilised the standard '5-cm method' for coil localisation (see Box 6.3). This method is dependent on the accurate localisation of the optimal site for stimulation of muscles in the hand contralateral to the site of stimulation. This typically occurs during the measurement of the RMT allowing a smooth transition to the measurement of the site of stimulation after this task has been undertaken. Although it was originally proposed that the 5-cm method would result in localisation of the stimulation coil over the dorsolateral prefrontal cortex (DLPFC), considerable doubt has been raised as to whether this occurs in most patients. DLPFC is typically defined by areas 9 and 46 in the Brodmann classification system. Some time ago, research demonstrated that the 5-cm technique would result in localisation of stimulation in DLPFC in only a minority of subjects [19]. In the majority of subjects, localisation was more posterior and occasionally more medial than the DLPFC. It is possible that DLPFC stimulation would result from the extension of the stimulation field into DLPFC from the more posteriorly located sites, but the intensity of this stimulation would be quite limited. Despite these concerns, clearly stimulation using the 5-cm technique has resulted in clinical efficacy in previous clinical trials. However, it may be possible to achieve greater clinical efficacy by modification of this technique.

In planning an approach that would potentially result in enhanced efficacy, the first consideration must be to define the area most likely to achieve beneficial clinical outcomes. The original target, DLPFC defined as Brodmann areas 9 and 46, is a quite large area of lateral prefrontal cortex overlapping superior, middle and parts of inferior frontal gyri. These Brodmann regions were characterised from analysis of a single post-mortem brain, and as such there is likely to be considerable error if directly applied to a broader range of subjects. A modern post-mortem study remeasured the site of areas 9 and 46 on multiple brains, producing a significantly more constrained area focused mainly on the superior frontal gyrus (area 9) in the middle frontal gyrus (area 46) [20]. One possibility is to try and anatomically target these regions. Another approach is to try and target a region based upon an identification of DLPFC abnormalities in the neuroimaging literature. However, a quantitative meta-analysis of neuroimaging changes in DLPFC in patients with depression did not suggest a clearly uniform target [21]. Given these concerns, few clinical studies have attempted to improve on the use of the 5-cm method. One study, using MRI-based neuronavigation, compared response to treatment localised using the 5-cm method to treatment localised to the junction of areas 9 and 46 based on the multiple-brain definition of these regions [22]. Promisingly, the study found enhanced clinical response with neuronavigationally targeted treatment to this site which was considerably more anterior

Box 6.3. 5-cm Method for Location of rTMS Treatment Site

1. Locate the cortical site for the optimal stimulation of hand muscles in the contralateral side (see Box 6.2 above).
2. Mark this site on the scalp.
3. Using a flexible measuring tape, measure 5 cm forward (or more as defined by protocol) from the motor site in a sagittal plane (see Fig. 6.4).
4. Mark the subsequent site.

Measuring the distance between this site and several anatomical landmarks (e.g. the preauricular and nasion points) will allow the remeasurement of this site without the localisation of the RMT on subsequent days.

and lateral than the site typically identified using the 5-cm method. However, these results have not been replicated to date.

If we do accept the results of this comparison, does it imply that neuronavigation is required to achieve enhanced treatment outcomes? It is possible that a similar improvement in outcome may be achieved with a more simple method that also results in more anterior and lateral treatment localisation and potentially also takes into account variation in head size, a clear deficiency of the 5-cm technique. One possibility that meets these criteria is the use of the system of measurement used for the 10–20 EEG system. The methods for establishing cortical sites with this system are relatively widely understood, and EEG coordinates can be reliably correlated with underlying cortical areas [23]. A site such as the F3 EEG point is known to relate to DLPFC and is likely to be more anterior than a 5-cm localised treatment point in most subjects. A simple guide for the measurement of the F3 site has been recently published [24] (see Fig. 6.5 for an overview of the standard method). It is also possible that enhanced clinical responses may be seen with a simple modification such as measuring 6 or 7 cm anterior to the motor site. Although such an approach still does not take into account individual differences in head size, it will ensure that treatment application does not differ too substantially from that used in clinical trials. This is a sensible approach until further studies establish the efficacy of more advanced methods of DLPFC localisation.

6.6.1 Clinical Recommendations

The typical approach to localise rTMS treatment is to target a point 5 cm anterior to the optimal site of stimulating hand muscles on the contralateral side. However, this does not allow for individual variability in head size. A sensible alternative is to extend this distance, possibly to 6 or 7 cm, especially in subjects with average to above average head circumference. The use of the F3 (and F4 on the right) EEG points as locations for treatment is also a sensible and conservative modification to this technique that could be adapted for clinical use.

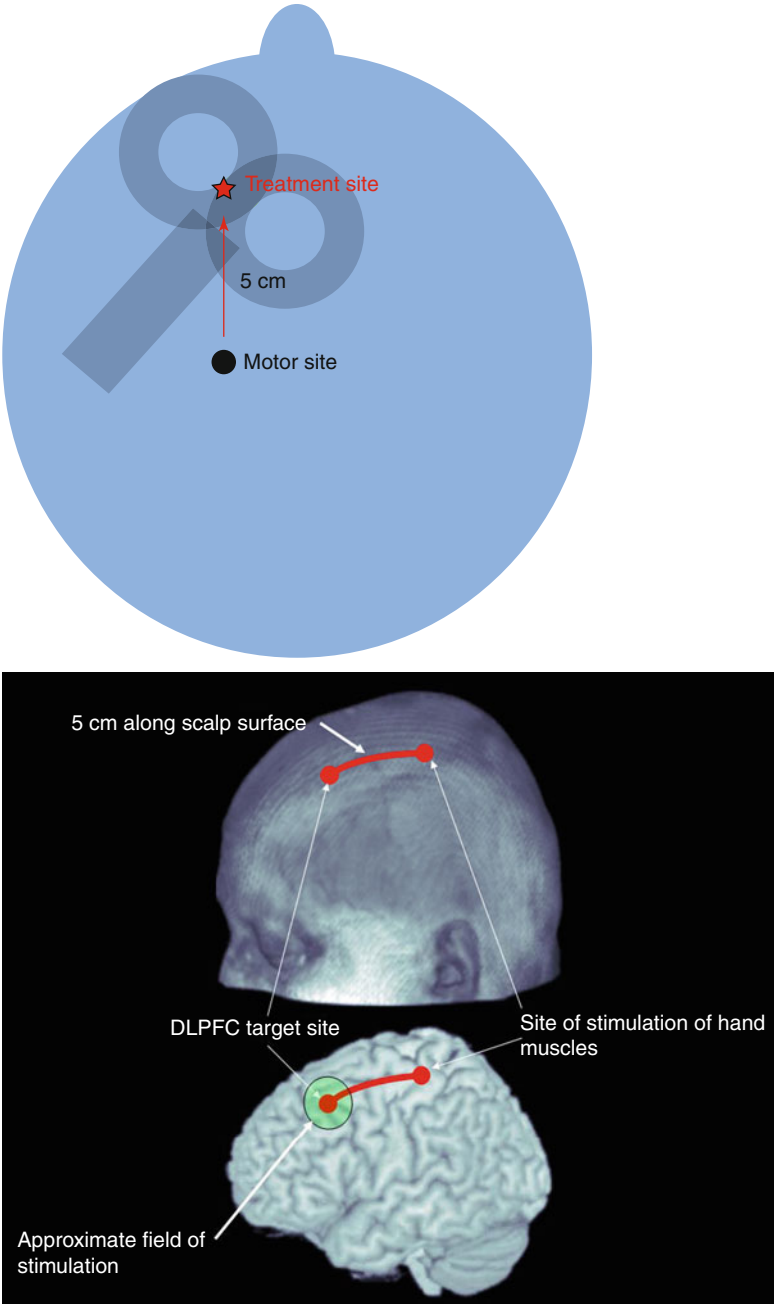

Fig. 6.4 The measurement of the 5-cm method for treatment site localisation

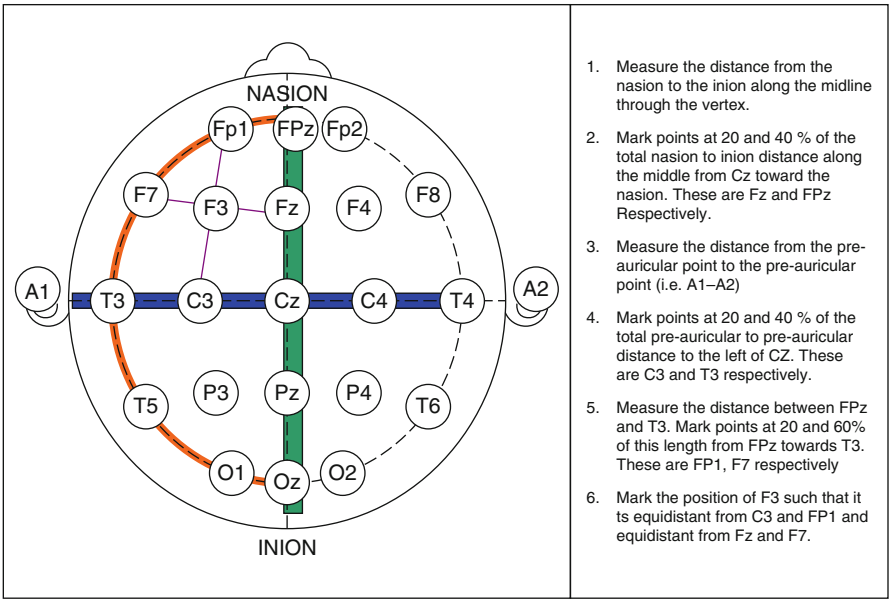

Fig. 6.5 Method for the measurement of the site of the F3 EEG point

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