Comparative incidence rates of mild adverse effects to transcranial magnetic stimulation

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Highlights

- We report the rate of mild adverse effects (MAEs) to transcranial magnetic stimulation over a four-year period at Cardiff University, across 1270 experimental sessions in healthy participants.
- Subsequent to both sham and active TMS sessions, we found an overall MAE rate of 5%; with the onset of 78% occurring after participants had left the laboratory.
- Additional analyses indicated that ~37% of MAEs reported may be associated with expectations or anxieties regarding TMS in naïve participants; routine monitoring of MAEs is recommended and screening documentation is provided.

Abstract

Objectives: Past research has largely neglected to investigate mild adverse effects (MAEs) to transcranial magnetic stimulation (TMS), including headache and nausea. Here we explored the relationship between MAEs, participant characteristics (age and gender) and protocol parameters, including mode of application, coil geometry, stimulated brain region, TMS frequency, TMS intensity, and active *vs.* sham stimulation.

Methods: Data from 1270 standardized post-monitoring forms was obtained from 113 healthy participants. Analyses aimed to identify the risk factors associated with MAE reports and specific symptoms.

Results: The overall rate of MAEs across TMS sessions was ~5%, with ~78% of symptoms occurring post-session. Initial TMS sessions were followed by a higher MAE incidence rate relative to later testing sessions. No associations between participant characteristics, TMS frequency, or intensity were observed.

Conclusions: TMS-related MAEs are relatively common and may be exacerbated by initial expectations or anxieties of participants. A significant proportion of MAEs may reflect reporting of coincidental phenomena that are unrelated to TMS. Recommendations for future safety studies are proposed and monitoring documentation is provided.

Significance: Our findings illustrate the importance of standardized monitoring of MAEs. Such research aids our understanding of how MAEs arise and may lead to interventions for reducing their incidence.

Keywords: transcranial magnetic stimulation; safety; mild adverse effects; post-monitoring; risk factors.

1. Introduction.

Through modulation of cortical activity, transcranial magnetic stimulation (TMS) has become an invaluable tool in experimental and clinical neuroscience (Rossi et al., 2009). Due to the relatively non-invasive nature of TMS, it has proven a favourable brain stimulation technique over many of its predecessors (e.g. electroconvulsive therapy: Loo et al., 2008; Pascual-Leone et al., 1993; Janicak et al., 2008). However, TMS is not without medical risks. Guidelines aimed at reducing the incident rates of the most severe known risk, TMS-induced seizure, have received careful attention (see Wassermann, 1998 and Rossi et al., 2009, for overviews). However, relatively little research has considered risk factors for more mild adverse effects (MAEs), including headache and nausea. This is particularly true for those MAEs that occur in the hours following the application of TMS, after the participant has left the laboratory. Investigating the origins of such risk factors may open avenues for reducing their incidence.

TMS exploits the principle of electromagnetic induction to produce small electrical currents in the cortex beneath the scalp site of stimulation (Wagner et al., 2009). The application of TMS not only generates electrical currents in brain tissue, but also in the intervening muscle and nerve fibres in the scalp (Rossi et al., 2009). This ancillary activation is the likely cause of tension headaches, local pain and peripheral muscle twitches (Wassermann, 1998; Pascual-Leone et al., 1993; Rossi et al., 2009). Local pain and headache, in particular, are the most common MAEs previously reported, affecting between 23% (Machii et al., 2006) and 40% of participants who receive repetitive (r)TMS (Rossi et al., 2009; Oberman et al., 2011). In addition, some reports suggest that symptoms may diminish with successive sessions (Machii et al., 2006; O'Reardon et al., 2007; Janicak et al., 2008). Here we further explore risk factors

that have been implicated in previous research as being causally or theoretically related to MAEs, including the mode of TMS application, intensity and frequency of stimulation, site of stimulation, coil geometry, auditory and tactile artefacts, and active *vs*. sham stimulation.

1.1. Mode of TMS application

Different neuronal effects can be achieved by administering TMS in various modes (Jahanshahi et al., 1997; Rossi et al., 2009). One approach involves the delivery of a single TMS pulse at times relative to stimulus onset (Amassian et al., 1989). Research into MAEs associated with single-pulse stimulation is limited, yet its application is considered to be relatively harmless (Jahanshahi et al., 1997). Indeed, the most recent international safety guidelines for TMS (Rossi. et al., 2009) merely note that neck pain, toothache and paresthesia (tingling sensation or numbness of the skin) are possible with single-pulse stimulation.

In contrast, greater attention has been paid to those protocols associated with a potentially elevated seizure risk, including rTMS and patterned theta-burst stimulation (TBS) (Machii et al., 2006). Both rTMS and TBS involve multiple TMS pulses in rapid succession to increase the effectiveness and duration of changes in cortical excitability (Jahanshahi et al., 1997; Macchi et al., 2006). Low discontinuation rates (primarily owing to MAEs) following rTMS are reported, with approximately 4.5% of all participants excluded from further participation (O'Reardon, et al., 2007; Janicak et al., 2008). Overall crude risk of MAEs after TBS has been estimated at ~5% (4.8% for healthy participants) with a crude risk per session of 1.1% (Oberman et al., 2011).

1.2. Intensity and frequency

Incidents of headache and local pain have been positively correlated with both the intensity of stimulator output and frequency of stimulation (Loo et al., 2008; Wassermann, 1998; Rossi et al., 2009[1]). Headaches have been reported after single-pulse TMS when suprathreshold intensities were administered (i.e. >100% motor threshold (MT): Rossi et al., 2009). Machii et al., (2006) speculate that the incidence of MAEs may be related to whether intensity of stimulation is set according to motor or phosphene thresholds (PT), noting that a greater stimulator output is often required to elicit phosphenes relative to motor responses.

1.3. Site of TMS application

Dense coverage of muscle nerve endings towards the front of the scalp may explain the greater incidence of headaches and local pain following frontal TMS in comparison to more medial or posterior sites (Wassermann, 1998; Machii et al., 2006; Loo et al., 2008). Frontal stimulation has also been associated with dental pain, due to aggravation of the trigeminal nerve (Ropohl et al., 2004). However, MAEs may also be induced by stimulation of posterior cortical sites. Satow et al., (2002) found incidents of nausea subsequent to right cerebellar stimulation in 2 of 8 participants who were administered low frequency rTMS, possibly owing to inadvertent stimulation of the posterior fossa. Neck pain has also been reported after TMS application to such posterior sites where the neck muscles can inadvertently be stimulated (Satow et al., 2002); however such effects could also be due to participants sustaining a constant head and neck position throughout an experimental session (Machii et al., 2006).

[1] Although see Machii et al., (2006) who report a greater incidence of symptoms in studies where TMS was applied at ≤1Hz stimulation in comparison to >1Hz stimulation for non-motor areas which. The authors attribute this to longer train durations in the use of lower frequencies.

1.4. Coil geometry

The shape and size of the coil used to administer TMS pulses has a direct influence on the spread of the induced electric field and the depth to which stimulation is possible, both in the cortex and on the scalp surface (Wagner et al., 2009). Theoretically, one might anticipate coil geometry to have a direct impact on MAEs, yet Rossi et al., (2009) argue that this is unlikely. However, the authors also recognise that no studies have tested this claim.

1.5. Auditory and tactile artefacts

The auditory artefacts of TMS increase with the intensity of stimulator output and can exceed 140dB (Counter et al., 1992; Rossi et al., 2009). Increases in auditory threshold or feelings of 'fullness in the ears' have been reported in instances where ear protection has not been used (e.g. Pascual-Leone et al., 1993). At the same time, the tactile artefact associated with peripheral nerve stimulation during TMS has been associated with paresthesia. As expected, this appears to be more frequent with rTMS as opposed to single-pulse protocols (Rossi et al., 2009).

1.6. Active vs. sham stimulation

Sham stimulation is often employed as a control condition in TMS studies. During sham, an active coil is oriented on the scalp in a way that produces little to no tactile effects but replicates the auditory artefact (Loo et al., 2000). Few reports overtly describe the details of the sham methods utilised. According to Lisanby et al., (2001), coil orientation for sham stimulation is critical in determining the density of the magnetic flux reaching the cortex. This complication would therefore also apply to muscle and nerve stimulation within the scalp tissue. MAEs have been reported after sham stimulation but are thought to be directly related to the orientation of the coil to the scalp surface (Loo et al., 2000). In a review of the

efficacy of rTMS in depression, Loo et al., (2008) concluded that 16% of patients reported headache after sham stimulation and 15% reported pain and/or discomfort (compared to 28% and 39% for active stimulation, respectively). However, the authors note that there was a decrease in these incidences associated with greater angular displacement from the scalp surface. Indeed, Lisanby et al., (2001) demonstrated that an active figure-8 coil oriented 90° to the scalp surface, with one wing touching the scalp, can reduce the energy reaching the cortex by 67-73% in comparison to an active coil placed tangentially on the scalp.

1.7. Limitations of previous research

As noted by Machii et al., (2006) and Oberman et al., (2011), there is a general lack of overt reports of MAEs within the TMS literature. Incident rates of MAEs may be underestimated as attention is understandably biased toward more serious adverse effects, including TMS-induced seizure. Studies that have explored MAEs tend to focus on one parameter at a time (e.g. mode of TMS application, see Oberman et al., 2011), rather than exploring the potential interactions between different parameters. Furthermore, incidents of adverse effects may have been missed as reports generally include only those symptoms that have occurred during a TMS session, ignoring side effects that may have a later onset. To enable precise causal inferences to be made regarding the origin of all adverse effects, standardized and rigorous monitoring of side effects is required (Machii et al., 2006; Oberman et al., 2011).

An additional concern is that the majority of literature reviews focus on clinical populations, either alone or in conjunction with reports from non-clinical populations (e.g. Loo et al., 2008; Oberman et al., 2011). Causation of adverse symptoms may therefore be clouded by potential neurological deficits or the effects of medication as opposed to the effects of TMS

per se. By focusing solely on non-clinical populations the baseline risk of MAEs may be uncovered.

1.8. The current study

Here we present data collected from standardized post-monitoring questionnaires, from TMS studies undertaken over a four-year period at the Cardiff University Brain Research Imaging Centre (CUBRIC). In contrast to previous studies, we adopted a comparative approach to explore the incident rates across a range of participant characteristics and protocol parameters. The aim of this systematic analysis was to uncover the TMS-related factors that most clearly predict MAEs. Furthermore, we not only studied symptoms reported during a session, but those that occurred in the 24-hour period following TMS.

2. Methods

2.1. Data inclusion and TMS parameters

Incidences of MAEs were documented for all TMS studies at CUBRIC between 2008 and 2012, inclusive. All experiments were undertaken for investigative as opposed to clinical purposes; the exploration of TMS-related MAEs was undertaken post-hoc and was not the primary objective of these studies. All experiments were approved by the local research ethics committee at the School of Psychology, Cardiff University. In total, post-monitoring forms for 1270 TMS sessions were included, across twenty-two studies.

In total, six different modes of TMS were applied to seventeen cortical sites. Either a circular coil (90mm) or a figure-8 coil (50mm or 70mm) was used to administer TMS via a Magstim Super Rapid or a Magstim Rapid² biphasic stimulator. All sessions were conducted with

single coils and all parameters were within the international safety guidelines of Wasserman (1998) and Rossi et al., (2009) (see Table 1 for all protocol parameters). All experimenters were trained to a standard level to ensure consistency in both the administration of TMS procedures and adherence to safety guidelines.

For 'active' TMS sessions the coil was oriented tangential to the scalp surface. All sham TMS sessions were conducted with the coil oriented 90° to the scalp surface. For figure-8 coils, one of the coil wings touched the scalp surface. To minimise direct cortical stimulation while maintaining any contact artefact, a 10mm acrylic plastic spacer was positioned between the coil and scalp for more powerful protocols (see Table 1) (Lisanby et al., 2001). Ear plugs were provided for all sessions in line with previous recommendations (Pascual-Leone et al., 1993; Wassermann, 1998; Rossi et al., 2009) and consecutive TMS sessions were separated by at least 24 hours.

[Insert Table 1 about here]

2.2. Participants

A total of 113 unique participants (69 female and 44 male) aged between 18 and 41 were recruited (M = 25.32, SD = 4.82). All participants were neurologically healthy and were screened for medical contraindications to TMS. Specifically, no participant was currently taking any neuroactive medication or had a history of frequent or severe headaches or migraines, drug abuse, brain injury or any other brain-related conditions (e.g. stroke or disease), or had a family history of seizure and/or epilepsy, or had sustained any head injury that had resulted in concussion or unconsciousness (see Appendix A for the specific screening questionnaire employed). Participants completed the screening questionnaire

during an induction interview with the experimenter and prior to participating in any new TMS studies. All participants had normal or corrected-to-normal vision. Participants took part in multiple studies (mean number of sessions participated in = 11.24, *SD* = 11.46) and informed consent was received prior to participation in each study. Immediately prior to receiving TMS, participants were further screened for state-dependent contraindications, including recent alcohol or recreational drug use, fatigue, or excessive consumption of caffeine (see Appendix B).

2.3. Recruitment Protocol and Intensity Setting

Prior to each study, all participants took part in a standard recruitment protocol involving:

a. An initial induction session: potential risks were explained, participants were screened (see above), and TMS was administered (~10 pulses administered in the vicinity of M1 at intensities 30-50% of stimulator output).
b. An intensity-calibration session: either via a distance-adjusted MT or PT (Stokes et al., 2005; Stokes et al., 2007; Varnava et al., 2011). MT was estimated using the observation of movement method (Kozel et al., 2000; McConnell et al., 2001; Varnava et al., 2011). TMS pulses were applied to the M1 region of the scalp to produce overt contractions in the contralateral hand. MT was defined as the intensity of stimulator output required to produce five observable contractions for every 10 TMS pulses, at the site where the most pronounced contraction was observed (Stokes et al., 2005). PT was determined similarly, with TMS pulses applied to the occipital cortex in order to induce the perception of a phosphene (Franca et al., 2006).
c. Comfort Threshold session: for more powerful protocols or those involving TMS to frontal sites, a comfort threshold was obtained *a priori* (see Table 1). To ensure that desired frequency and intensity of TMS was not uncomfortable for the participant.

Intensity was adjusted on a site-specific basis and then matched between sites according to the lowest comfortable intensity. During comfort threshold acquisition, test pulses were applied to the desired site and frequency for that protocol. A staircase method was employed in which the stimulator output was varied until the comfort threshold was reached; this was either the target intensity required for that protocol or the point where discomfort was reported. Critically, if discomfort was reported before the target intensity was reached, where possible the target intensity was lowered (see Table 1), otherwise participants were excluded from further participation in that particular study.

2.4. Post-monitoring

A standard post-monitoring (PM) form was provided to participants after each TMS session to assess whether they had experienced any MAEs during the session or in the following 24-hours. Participants were specifically asked whether they had experienced any incidence of seizure, fainting or collapse, dizziness, nausea or vomiting, headache, muscular aches, muscle spasm or twitches, insomnia, sensory problems, difficulties speaking or understanding speech, lack of coordination, or slowness or impairment of thought (see Appendix C). Participants were also encouraged to document any MAEs they had experienced other than those listed. Further information concerning the nature of adverse symptoms (e.g. longevity or severity) was documented where possible.

2.5. Statistical Analyses

Analyses focused on whether specific participant characteristics (gender and age) or protocol parameters (mode of TMS application, site of stimulation, coil geometry, frequency, intensity, and active *vs.* sham stimulation) were relevant risk factors for MAEs. Age of participant at time of involvement was separated into one of two categories: either above or

below the mean. The categorisation of mode of application, site of stimulation and coil geometry can be found in Table 1. Duration of TMS was categorised as either short duration (i.e. 3 minutes or less) or long duration (i.e. 1 hour or more; see Table 1). Intensity of stimulation was explored in respect to the absolute percentage of stimulator output, or indexed as a percentage of MT or PT. If protocol intensities were based on MT or PT, then intensities were categorised as either sub-threshold (i.e. <100%MT or PT) or supra-threshold (i.e. ≥ 100%MT or PT). Where active and sham conditions were present in the same session the corresponding PM form was treated as 'active'. Sham data was not included in any 'stimulation site' analyses as coil positioning may not be exact (either placed on an arbitrary basis or based on an 'average' location where more than one cortical site was stimulated in a protocol). A minimum alpha level of .05 was applied to all statistical tests. Due to the categorical nature of the data, a mixture of binomial and multinomial logistic regression analyses were employed, followed by non-parametric inferential statistics (chi-square; and Fisher's Exact tests where expected frequencies were less than 5). Analyses were conducted at two levels:

1. *Analysis at the level of reports*: data from all PM forms were analysed to explore the risk factors (participant and protocol parameters) across 1270 MAE reports. This level of analysis focused on whether one or more MAEs were reported or not, as opposed to the specific type of MAE.
2. *Analysis of specific MAEs*: data from PM forms where adverse symptoms were reported were analysed. This level of analysis sought to explore whether specific parameters were associated with specific side effects. To reduce statistical limitations caused by limited spread through key regions of the data set, adverse symptoms that were likely to co-occur were categorically merged. These categories were: *headache*; *nausea* (including

dizziness, nausea and vomiting); *muscular problems* (including muscular aches, spasms and twitches); and *other* (including lack of co-ordination, sensory problems, slowness or impairment of thought, insomnia and any other symptoms not pre-categorised).

3. Results

3.1. Analysis at the level of reports

[Insert Table 2 about here]

Table 2 presents the frequency and category of all reported MAEs and the corresponding protocol details. No incidents of seizure or auditory side-effects were observed. Of the 1270 PM forms collated, 546 sessions were undertaken by male participants, and 724 by female participants. Table 3 shows the percentage use of each parameter across all PM forms. MAEs were reported on 62 PM forms (4.88%; with 78 symptoms reported in total, see Section 3.2.). In total, 44 of the 113 participants who took part in these experiments reported at least one MAE (39%). Even though the proportion of participants that reported MAEs was substantial, exclusion rates were modest. Only 5 participants were excluded from further participation after an initial session, and 10 from later experimental sessions. These exclusion rates indicate that the majority of MAEs were very mild (e.g. a slight headache as opposed to more severe sensory or muscular problems- see Table 2) and participants expressed a clear intent to continue. MAE data relating to all participants were retained in the analyses unless otherwise specified.

3.1.1. Active vs. sham TMS

Although more MAEs were associated with active reports (5.38%) than with sham reports (2.09%), preliminary analysis revealed this difference to be of only marginal significance ($\chi^2(1, N=1270)= 3.76, p=.052$). Where active and sham sessions were completed separately, all protocol parameters were matched, with the obvious exception that there was no direct cortical stimulation associated with sham sessions (see Table 1). By analysing active and sham PM forms separately, insights into MAEs that are associated with TMS testing procedures rather than TMS *per se* may be uncovered.

[Insert Table 3 about here]

3.1.2. Active reports

Data relating to all participant (gender and age) and protocol variables (mode of application, site of application, coil geometry and duration of stimulation) for active TMS sessions were entered into a backward stepwise binary logistic regression analysis to determine whether any of these variables could predict whether an MAE was reported. A significant model (χ^2 (5, N=1079)=18.24, p=.003) was revealed, in which mode of TMS application was the only significant contributor (Wald χ^2 (5, N=1079)=16.77, p=.005; Nagelkerke's R^2=.049). This effect was driven solely by TBS (β=3.81; Wald χ^2 (1, N=1079)=13.44, p<.001). As shown in Table 3, TBS accounted for a similar number of PM forms to single-pulse applications, but the percentage of MAEs found within each mode of application was lower for TBS than for other modes. Therefore TBS appears to be an important predictor for *reduced* occurrence of MAEs. Subsequent chi-square analyses confirmed a significant association between all modes of TMS application and MAEs (p=.003, Fisher), with a significantly greater percentage of MAEs associated with single-pulse sessions relative to TBS sessions (9% and

3%, respectively; χ^2 (1, *N*=777)=15.27, *p*<.001). No other significant association between adverse reports and mode of application was found.

The reduced occurrence of MAEs associated with TBS may be due to the typically low absolute stimulator intensities at which these protocols are applied (see Table 1). Intensity and frequency data were substituted into the regression analysis in place of mode of application (gender, age, site of application, coil geometry and duration of stimulation remained). To circumvent potential issues of multiple collinearity between these variables (r= -.62, *p*<.001), separate regression analyses were carried out including frequency and then intensity. No significant regression models were observed. Due to initial induction and intensity-calibration sessions, many of the single-pulse protocols yielded little frequency and intensity information (see Method section 2.3. and study 22, Table 1). Further exploration of the data suggested that the higher incidence of MAEs associated with single-pulse sessions was the result of all participants completing an initial single-pulse session prior to further experimental participation (i.e. an induction session, or sessions involving the acquisition of MT or PTs[2]). Indeed, significantly more MAE reports were associated with initial single-pulse sessions (40%) as opposed to later active TMS sessions (12%; χ^2(1, *N*=1079)= 33.97, *p*<.001). MAEs reported after later experimental protocols may be confounded by the omission of five participants who had experienced an MAE of sufficient severity to warrant complete exclusion; this effectively prevented these participants from contributing further to incidence rates for MAEs. However, removal of these participants from the data had no demonstrable effect on the regression model (modelχ^2 (5, *N*=1072)=48.35, *p*=.001, Nagelkerke's R^2=.14; mode of application: Waldχ^2 (5, *N*=1072)=13.69, *p*=.02; TBS: β =3.63; Waldχ^2 (1, *N*=1072)=10.97, *p*=.001) or subsequent association analyses (mode of

[2] For all analyses initial sessions are inclusive of induction session and participant's initial MT or PT.

application: p=.02, Fisher; single-pulse *vs.* TBS: χ^2 (1, N=770)=11.48, p=.001), with a greater number of MAEs still associated with single-pulse sessions (8%) relative to TBS sessions (3%).

This greater proportion of MAEs within initial sessions may reflect a particular sensitivity to MAEs in naïve participants. To test this possibility, the regression analyses were repeated with all initial sessions excluded. The entry of all of the participant or protocol variables (gender, age, mode of application, site of application, coil geometry and duration of stimulation) led to a non-significant regression model and no significant associations between mode of application and MAEs (p=.52, Fisher).

Differences in the overall duration of TMS between single-pulse and TBS application, or the preclusion of potential MAEs by excluding participants who do not pass a comfort threshold do not appear to be adequate alternative explanations for these findings. Although the duration of stimulation for TBS protocols was shorter than that for single-pulse protocols (see Table 1), duration of stimulation was not shown to be a significant predictor of MAEs in any of the regression analyses. In addition, the effects of comfort threshold did not account for differences in MAEs between single-pulse TMS and TBS. Although excluding those participants that did not pass a comfort threshold may, in effect, prevent them from contributing to MAEs in that study, no difference in the associations were found between MAEs and whether or not a comfort threshold was conducted (χ^2(1,N=804)= .78, p=.38[3]). These results further indicate that incidence of MAEs was greater following initial single-pulse sessions compared with later experimental sessions, which may indeed reflect an initial sensitivity to MAEs in naïve participants.

[3] All inductions, MTs and PTs were excluded from these analyses, as CT sessions would be based on the intensities calibrated as a result of these sessions.

The application of TMS at supra-threshold intensities (i.e. ≥100%MT or PT) may account for why there is such a high incidence of MAEs associated with initial single-pulse sessions. Supra-threshold stimulator intensities are likely to have been applied during intensity-calibration sessions (see Method section 2.3.b). Although the specific intensities used in these intensity-calibration sessions was not recorded, analyses revealed no significant association between MAE incidence and whether the intensities used in later testing sessions were set above or below MT (p=.83, Fisher) or PT (p=.25, Fisher), or matched to MT or PT (p=.79, Fisher). These results indicate that variance in stimulator output relative to the excitability threshold is not reliably predictive of MAEs, but that MAE reports are, once again, more likely to be driven by the initial sensitivity to TMS in naïve participants.

This premise is further illustrated through analyses regarding MAEs and cortical site of stimulation. Although site of stimulation was not a significant predictor of MAEs in any of the regression analyses, further exploration revealed a significantly higher rate of MAEs associated with the threshold sites of M1 and occipital sites combined (10%) *vs*. all other sites (3%; $\chi^2(1, N=1079)=21.60, p<.001$), for M1 alone (10%) *vs.* all other sites (4%; $\chi^2(1,N=1079)=13.48, p<.001$), and for occipital stimulation alone (9%) *vs.* all other sites (5%; $\chi^2(1,N=1079)=4.25, p=.04$). Yet no significant difference was found between M1 and occipital sites and their association with MAEs (10% and 9%, respectively; χ^2 $(1,N=378)=.08$, p=.77).

3.1.3. Sham reports

All analyses completed with active reports were repeated with sham reports only. There was no significant association between incidence of MAEs and any of the participant variables

(gender or age) or protocol variables (mode of application, site of application, coil geometry and duration of stimulation, frequency or absolute intensity; $p>.37$, Fisher, for all analyses). Of the 191 PM forms completed subsequent to sham stimulation, MAEs were only reported on 4, and all corresponded to TBS administration (see Table 2). Similar rates of MAEs were associated with active TBS sessions (2.59%) and sham TBS sessions (2.09%). There was no significant difference in the association of active *vs.* sham TBS and MAEs ($p>.99$, Fisher), demonstrating that the incidence of these MAEs may have been coincidental or due to factors unrelated to direct cortical stimulation.

3.2. Analysis of specific MAEs

When considered at the level of reports (via PM forms), the incident rates of MAEs are likely to be underestimated. This is due to the exclusion of participants who report MAEs early in the sequence of experimental sessions and the repeated sampling of those participants who never report MAEs. Therefore we tested whether specific symptoms were associated with particular participant characteristics (gender or age) or protocol parameters (mode of application, site of application, coil geometry and duration of stimulation, frequency or absolute intensity; see Method section 2.5 for classification of adverse symptoms).

This level of the analysis included 44 participants. Across all reports, participants completed between 1 and 41 sessions each ($M = 11.32$, $SD = 11.07$). Analyses were based on 78 symptoms reported in total, owing to multiple symptoms reported on 12 of the 62 adverse PM forms. Of the 44 participants who had experienced MAEs, 42 had experienced these following active TMS rather than sham. Eleven participants reported further MAEs after subsequent protocols, accounting for 25 of 62 sessions that provoked MAEs (mean number of sessions with MAEs = 3.18, $SD = 1.40$), implying a predisposition for MAEs in some

participants. Indeed, MAEs were reported after 20% of all sessions for those experiencing multiple MAEs, compared to 10% for participants who reported MAEs after a single session. This difference was reliable ($\chi^2(1,N=498)=8.87$, $p=.003$) even though there was no significant difference in the number of sessions completed by each group ($t(42)=1.46$, $p=.68$).

Removal of the initial sessions from the data still indicated that there was a general predisposition in some participants to experience MAEs ($\chi^2(1,N=449)=12.82$, $p<.001$). For those participants who reported symptoms after more than 1 session, 18% of completed sessions now included MAEs, compared with 6% for participants who reported MAEs after a single session. For those participants that experienced MAEs, more reports were associated with single-pulse (82%) sessions as opposed to experimental sessions (9%; $\chi^2(1,N=498)=40.12$, $p<.001$).

There was no difference in the distribution of MAEs across categories reported during initial sessions *vs.* experimental protocols ($p=.79$, Fisher).

3.2.1. Active vs. sham

Analysis of active *vs.* sham data did not reveal any significant difference in associations with each category of MAEs ($p=.61$, Fisher). Symptoms reported subsequent to sham stimulation were all reported by participants who had experienced multiple symptoms. To reduce statistical limitations caused by limited spread through key regions of the data set (as sham data was based on only 4 positive PM forms), analyses were carried out both exclusive and inclusive of sham data.

3.2.2. Analysis of specific MAEs excluding sham TMS

Figure 1 shows the overall percentages of each category of adverse symptoms reported. Due to the infrequent use of each protocol parameter across studies in this level of the analysis, only gender and age could be included in a multinomial regression analysis, neither of which reliably predicted the reported MAE category (Model $\chi^2(6,N=74)=7.23$, $p=.301$; Nagelkerke's $R^2=.10$). No significant associations between type of MAE reported and protocol variables was found (mode of TMS application, $p=.34$, Fisher; or coil geometry, $p=.89$, Fisher). There was no difference in the category of MAE associated with initial or later sessions ($p=.66$, Fisher).

[Insert Figure 1 about here]

Since these studies included stimulation of a wide range of cortical regions, we also explored the potential association between specific symptoms and cortical sites based on previous literature (e.g. Wassermann, 1998; Satow et al., 2002; Machii et al., 2006; Loo et al., 2008). In contrast to previous expectations, incidence of headache was not significantly associated with frontal stimulation[4] compared with all other symptoms and sites ($\chi^2(1,N=74)=.51$, $p=.48$) However, in accordance with Satow et al., (2002) nausea was more likely to be associated with occipital stimulation compared with all other symptoms and sites ($\chi^2(1,N=74)=4.54$, $p=.03$); with nausea reported in 43% of MAEs associated with occipital stimulation, compared with 19% for other sites. Circular coils were more frequently used in protocols targeting occipital regions but coil geometry was not associated with nausea symptoms in comparison to other symptoms ($p=.36$, Fisher).

[4] Here, frontal sites were classified as those cortical sites anterior to and inclusive of the motor cortex.

3.2.3. Analysis of specific MAEs including sham TMS

All analyses completed exclusive of sham data were repeated with sham data included. No significant predictors of, or associations with, specific MAE category were observed (p>.59, Fisher, for all analyses).

3.3. Onset of specific MAEs

Of all 78 symptoms reported (over both active and sham sessions), 14 (18%) were reported to be present during the session only, and 61 (78%) reported only in the 24 hours after TMS. The remaining symptoms of nausea, dizziness and headache were reported subsequent to a single TMS session and occurred both during the session and in the following 24 hours.

4. Discussion

The aim of this study was to provide comparative incidence rates for a range of MAEs associated with TMS. The overall incidence rate of MAEs across sessions is comparable with previous reviews of TBS protocols, converging on ~5% (e.g. Oberman et al., 2011). Although this figure may represent an underestimation of TMS-induced MAEs (see Results 3.2), the incidence rates across participants (39%) are comparable to previous reports (e.g. Machii et al., (2006) report that 40%+ of participants experience MAEs after rTMS). In line with previous findings, headaches were found to be the most common MAE (e.g. Machii et al., 2006; Loo et al., 2008; Rossi et al., 2009; Oberman et al., 2011). In contrast to previous safety studies, we undertook a comparative post-hoc approach in which the effects of participant and protocol parameters were considered. Previous studies and literature reviews have either reported only the quantity and type of incidents, or have explored risk factors associated with one mode of TMS application (e.g. Machii et al., 2006; Oberman et al.,

2011). Additionally, this study was completed based on data collected from neurologically healthy participants, in contrast to previous studies that also included data from clinical populations (e.g. Machii et al., 2006; Oberman et al., 2011).

Our results differ somewhat from previous observations that MAEs were more likely to occur after rTMS or TBS than after single-pulse TMS (e.g. see Rossi et al., 2009). The majority of MAEs observed here were associated with single-pulse stimulation, as opposed to alternative protocols previously reported as carrying a higher risk (Machii et al., 2006). Our findings suggest that the greater frequency of MAEs associated with single-pulse sessions may be due to increased sensitivity in naïve participants to MAEs prior to initial TMS sessions (i.e. induction, MT or PT sessions) as opposed to subsequent experimental protocols. Data including initial single-pulse sessions indicated that TMS of M1 and occipital cortex (MT and PT sites), considered either separately and in conjunction, were associated with a greater incidence of MAEs compared with all other sites. However, no such difference was found between M1 and other cortical sites during later experimental sessions.

These findings cannot be explained by duration of stimulation during a session, or comfort threshold exclusions (i.e. the exclusion of participants from a study if they found the desired frequency and intensity of TMS uncomfortable; see Method section 2.3.c), as these factors were assessed in our analyses. Instead it seems likely that naïve participants may have expectations or anxieties about the sensations and subsequent side effects of TMS, leading to relatively higher reporting of coincidental phenomena. Past research has indicated that the incidence of MAEs may be reduced with successive testing sessions (O'Reardon et al., 2007; Machii et al., 2006; Janicak et al., 2008). This may well be due to the reduction in anxieties and expectations regarding TMS application over time.

It is notable that some MAEs were reported subsequent to sham stimulation. The magnetic flux reaching the scalp and cortex for sham conditions presented here is negligible due to the coil orientation implemented and the use of acrylic plastic spacers for more powerful protocols (see Lisanby et al., 2001). It appears that incidence of sham-related MAEs for TBS sessions may be coincidental or related to TMS-evoked anxiety or other non-specific stressors present in experimental situations. To unearth whether MAEs are due to physiological factors or the reporting of coincidental phenomena, future research could explore MAEs between different experimental settings (e.g. involving EEG or MRI). If TMS-evoked anxiety is the origin of some MAEs, then future research would benefit from personality profiling through anxiety-related measures prior to participation. Although some clinical safety studies report the use of psychometric questionnaires (e.g. Loo et al., 2008), there has been no direct exploration of whether MAEs correlate with such measures.

Although the risk of MAEs is higher in clinical populations (Oberman et al., 2011), it is unclear whether this is due to the expression of anxiety-related traits and differential expectations of TMS in clinical groups/settings, or the underlying pathophysiology of the disease-state and concurrent use of medication (Machii et al., 2006; Loo et al., 2008). The inclusion of personality measures, and comparative research based on clinical and non-clinical populations, could help untangle the contribution of these factors.

Aside from the effects of initial session sensitivity, analyses indicated that MAE incidence rates found in subsequent experimental protocols were more likely to be associated with occipital stimulation compared with other cortical sites. This observation is consistent with previous findings by Satow et al., (2002) and suggests that occipital stimulation could lead to

activation of the posterior fossa, resulting in nausea symptoms. Importantly, comfort thresholds were not used in any of our experimental protocols targeting occipital cortex. The screening of participants using comfort thresholds prior to such applications would be expected to enhance participant comfort and may provide a sufficient intervention to reduce or eliminate such MAEs.

Our study presents a post-monitoring approach to TMS safety research. While this comparative approach assesses the rate of MAEs across a range of participant and protocol parameters, it is important to note that our findings emerged from post-hoc analyses within studies where uncovering the basis of MAEs was not the main objective. By grouping different protocols, the analyses are compiled across varying stimulation approaches. The conclusions we make with regards to the influence of specific parameters (e.g. frequency, intensity, etc) on TMS-related MAEs are therefore, to an extent, tentative; particularly when considering the application of rTMS and TBS. Before concrete inferences can be made, it is important that variations in these parameters are explored directly. For a more complete understanding of the complex nature of TMS-related MAEs, future studies could be specifically designed for that purpose using factorial *a priori* designs (e.g. Satow et al., 2002).

In conclusion, it is reasonable to expect the focus of research to be centred on TMS protocols associated with the most severe adverse effects, including seizure. However, exploration of protocols associated with more common MAEs should not be undervalued when ensuring participant comfort and safety. This study highlights the importance of monitoring MAEs to TMS. Moreover, not all MAEs occurred during a TMS session; instead, the onset of most symptoms was reported post-session (~78% of MAE reports). The advantages of

standardized post-monitoring are manifold and we recommend that post-screening be adopted broadly in TMS studies. Participant responses to follow-up questionnaires may be more informative when probing whether any of a range of specific symptoms was experienced after the previous TMS session as opposed to only during the session. Standardized post-monitoring across all sessions will thus enhance the inferences made in future comparative studies and meta-analyses. In accordance with the recommendations by Machii et al., (2006) and Oberman et al., (2011) documentation of specific participant characteristics and protocol parameters will add to our understanding of the origin of MAEs and may lead to interventions for reducing their likelihood.

Acknowledgements

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Figure 1. Percentages of each category of MAE reported across all post-monitoring forms (including both active and sham data).

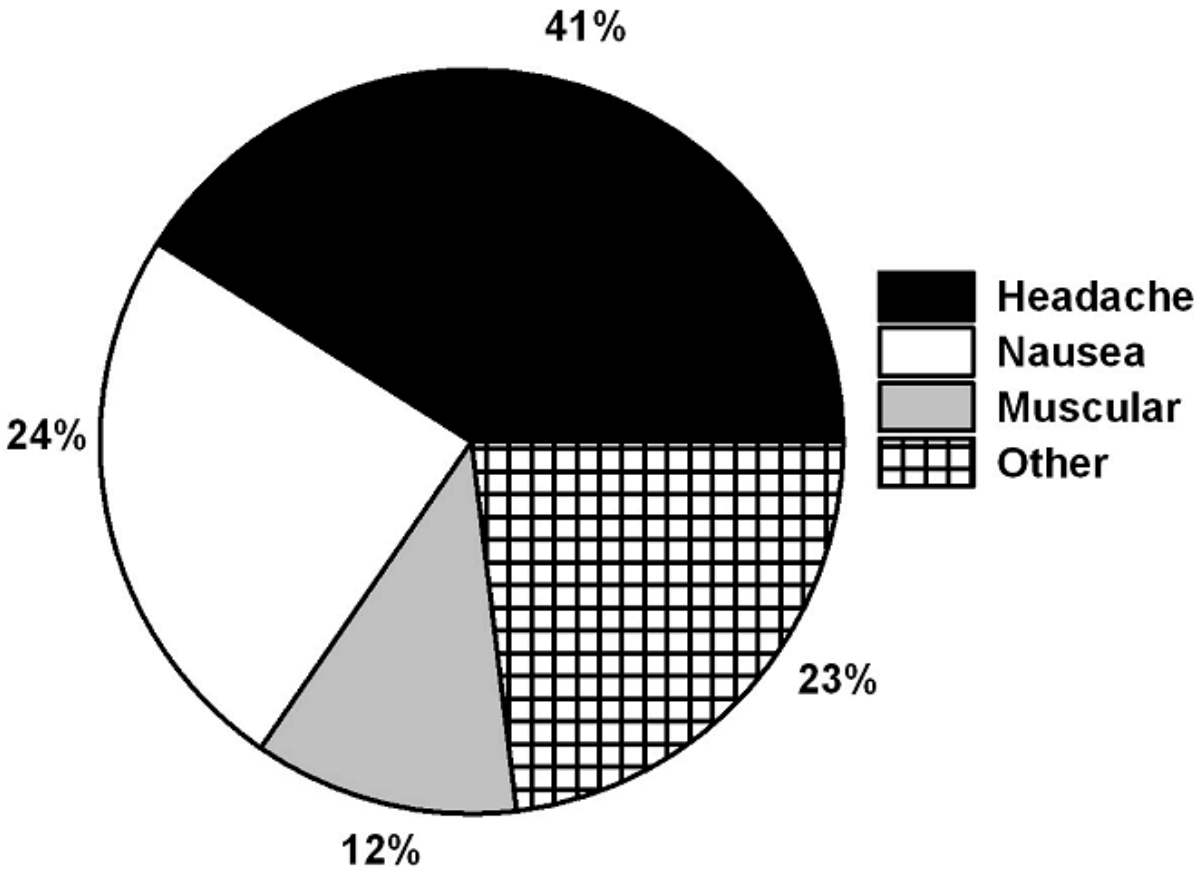

Table 1
The protocol parameters associated with each study. Two forms of TBS were administered: continuous and intermittent (600 pulses in 40 s and 600 pulses over 3 min, respectively as described in Huang et al., 2005). For the purposes of assessing the association of TBS with MAEs, these protocols were collapsed into a single 'TBS' condition.*

Study	Mode	Site	Coil	Duration	Abs. Intensity	%MT/%PT**	Freq.	*n*	Sessions	Sham	Spacer	CT
1	Double	r-aIPS, r-pIPS	Fig-8	1 h+	36–83%	120%MT	10	23	45	No	N/A	No
2	Single	V1 (calcarine)	Circ	1 h+	47–70%	120%PT	N/A	5	42	Same	Yes	No
3	Sing + doub	V1 (calcarine)	Circ	1 h+	70%	120%PT	25	1	12	Same	No	No
4	Sing + doub (+single alone)	Occ (pole), V1 (calcarine)	Circ	1 h+	25–70%	95%PT	25	22	85	Same	No	No
5	cTBS	r-IFG, r-IFJ	Fig-8	40s	23–46%	59–80%MT	50	11	37	Sep	Yes	Yes
6	rTMS	r-AG	Fig-8	1 h+	37–86%	110–160%MT	25	31	68	Sep	No	Yes
7	cTBS	r-DLPFC, r-IFG	Fig-8	40s	25–45%	65–80%MT	50	9	27	Sep	Yes	Yes
8	iTBS	l-DLPFC	Circ	3mins	21–49%	49–82%MT	50	32	79	Sep	Yes	Yes
9	cTBS	AG (left and right)	Fig-8	40s	17–58%	80%MT	50	25	75	Sep	Yes	No
10	cTBS	r-aIPS, r-pIPS, r-FEF	Fig-8	40s	19–50%	70–80%MT	50	23	135	Sep	Yes	Yes
11	Single	r-FEF, r-IFG, r-PPC	Fig-8	1 h+	36–70%	90–120%MT	N/A	19	49	Same	No	Yes
12	cTBS/rTMS	l-IFG	Fig-8	40s/ 1 h+	19–89%	80–140%MT	5–50	19	49	Sep	No	Yes
13	Double	Occ (pole)	Fig-8	1 h+	50–70%	93–120%MT	20	13	24	Same	No	Yes
14	c/iTBS	V1 (calcarine)	Circ	40s/3mins	32–42%	80%MT	50	7	9	Sep	Yes	No
15	c/iTBS	Occ (pole), V1 (calcarine)	Circ	40s/3mins	26–50%	80%MT	50	26	101	Sep	Yes	No
16	cTBS	r-IFG, r-IFJ, r-SMA	Fig-8	40s	20–39%	51–80%MT	50	19	65	Sep	Yes	Yes
17	cTBS + Sing	Occ (pole), V1 (calcarine)	Circ	1 h+	52–87%	80%MT	50	12	24	Same	No	No
18	Single	r-IFG, r-IFJ	Fig-8	1 h+	34–45%	100–105%MT	N/A	3	7	Sep	No	Yes
19	rTMS	r-aIPS, r-pIPS, r-SMG	Fig-8	1 h+	45–65%	71–122%MT	10	8	19	Same	Yes	Yes
20	rTMS	r-Parietal, r-SMA	Fig-8	1 h+	56–87%	142.5%MT	1	7	17	Sep	Yes	Yes
21	rTMS	Occ (pole)	Fig-8	1 h+	22–75%	100–115%MT	10	13	26	N/A	N/A	No
22	Single	M1/Occ (left and right)	Fig-8	1 h+	N/A	N/A	N/A	104	275***	N/A	N/A	N/A

* Nb. Mode = mode of TMS application; Double = double pulse; Single = single pulse; Sing + doub = single and double pulse; cTBS = continuous theta-burst stimulation; iTBS = intermittent theta-burst stimulation; rTMS = repetitive transcranial magnetic stimulation; cTBS + Sing = continuous transcranial magnetic stimulation and single pulse; c/iTBS = continuous or intermittent theta-burst stimulation; Site = site of TMS application; l- = left hemisphere; r- = right hemisphere; IFG = inferior frontal gyrus; IFJ = inferior frontal junction; AG = angular gyrus; aIPS = anterior intraparietal sulcus; pIPS = posterior intraparietal sulcus; FEF = frontal eye field; PPC = posterior parietal cortex; Occ = occipital; M1 = primary motor cortex; SMA = pre-supplementary motor area; SMG = supramarginal gyrus; Coil = coil geometry; Circ = circular coil; Fig-

Table 2
The frequency of the occurrence of each adverse symptom reported with relevant protocol details. For definitions see * below and *Nb. for Table 1.

Mode	Site	Coil	Active	Freq	Intensity	Duration	Incidents per category				Additional information for 'other' symptoms
							Head	Nausea	Musc	Other	
Single	M1	Fig-8	Active	N/A	N/A	1 h+	11	5	5	8	Sensation in wrist/hand (4); insomnia (1); bruising sensation/ pain at site of TMS(2); lack of coordination (1)
	Occ	Fig-8	Active	N/A	N/A	1 h+	4	2		2	Tingling body sensation(1); nosebleed (1)
	Occ	Circ	Active	N/A	N/A	1 h+	2		2	2	Sensory problems (1); slowness of thought (1)
	FEF	Fig-8	Active	N/A	120%MT	1 h+	1				
	IFG	Fig-8	Active	N/A	95–100%MT	1 h+	2				
	PPC	Fig-8	Active	N/A	95%MT	1 h+	1	2			
Double	aIPS	Fig-8	Active	10 Hz	120%MT	1 h+		1			
	pIPS	Fig-8	Active	10 Hz	120%MT	1 h+				1	Jawache (1)
cTBS + Sing	Occ	Circ	Active	50 Hz	80%MT	1 h+		1			
rTMS	AG	Fig-8	Active	25 Hz	160%MT	1 h+	3				
	aIPS	Fig-8	Active	10 Hz	119%MT	1 h+				1	Lack of co-ordination (1)
	Occ	Fig-8	Active	10 Hz	100–115%MT	1 h+		3			
Sing + doub	V1	Circ	Active	25 Hz	95%PT	1 h+	3	1			
c/iTBS	aIPS	Fig-8	Active	50 Hz	80%MT	3 min max			1		
	FEF	Fig-8	Active	50 Hz	80%MT	3 min max	1				
	IFG	Fig-8	Active	50 Hz	80%MT	3 min max	1				
	IFJ	Fig-8	Active	50 Hz	62% MT	3 min max				1	Tingling sensations on left side of body (1)
	V1	Circ	Active	50 Hz	80%MT	3 min max		1		1	Temporary speeded thoughts/actions (1)
	Occ	Circ	Active	50 Hz	80%MT	3 min max		3			
	DLPFC	Circ	Active	50 Hz	78–80%MT	3 min max	1			1	Tiredness post-session (1)
	Sham	Circ	Sham	50 Hz	80%MT	3 min max	2				
	Sham	Fig-8	Sham	50 Hz	25–80%MT	3 min max	1			1	Insomnia (1)
	Total number of each adverse symptom						33	19	8	18	

* Nb. Head = headache; Musc = muscular problems; 3 min max = maximum of 3 minutes of stimulation.

Table 3
The percentage use and the corresponding percentage of MAEs within each mode of TMS application, each site of stimulation and each coil geometry. Values are shown separately for both active and sham stimulation. For definitions see * below and *Nb. for Table 1.

	Mode						Site**					Coil	
	Single	TBS	rTMS	Sing + doub	Double	cTBS + Sing	Post	Frontal	M1	Occ	Sham	Fig-8	Circ
% Use													
Active	36.24	35.77	12.14	7.23	6.4	2.22	35.19	19.69	18.66	11.42	15.04	73.68	26.32
Sham	0.52	90.58	8.9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	64.4	35.6
% MAEs													
Active	9.21	2.59	4.58	3.85	2.9	4.17	2.91	3.2	10.13	8.97	2.09	5.79	4.23
Sham	0	2.31	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.63	2.94

* Nb. Post = cortical sites located posterior to M1; Frontal = cortical sites located anterior to M1.

** For efficiency of presentation, cortical sites are divided into Frontal areas (located anterior to the motor cortex); and Posterior areas (located posterior to the motor cortex). M1 and occipital stimulation are shown separately as these sites were stimulated most frequently in initial single-pulse sessions. Due to the arbitrary nature of the positioning of the coil for sham stimulation, these sessions are shown as a separate cortical 'site'.

TMS SCREENING FORM

NAME OF PARTICIPANT …… Sex: M / F

Left or right handed?……

Date of birth……

Do you normally wear glasses or contact lenses? (please indicate which)……..

Do you have normal colour vision?…….

Transcranial Magnetic Stimulation (TMS) is a method for producing an electric current in a small part of the brain. During TMS, a current passes through a copper coil that is wound inside a plastic casing and held over the participant's head. The current in the coil produces a magnetic field, which passes safely through the scalp and causes electrical activity in brain tissue.

Before receiving TMS, please read the following questions carefully and provide answers. For a small number of individuals, TMS may carry an increased risk of causing a seizure. The purpose of these questions is to make sure that you are not such a person. You have the right to withdraw from the screening and subsequent scanning if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions.

If you are unsure of the answer to any of the questions, please ask the person who gave you this form or the person who will be performing the study. Definitions of some of technical terms are given overleaf.

	Please tick
Have you ever had an adverse reaction to TMS?	☐Yes ☐No
Do you experience claustrophobia?	☐Yes ☐No
Have you or has anyone in your family had a seizure?	☐Yes ☐No
Have you had a stroke?	☐Yes ☐No
Have you had a serious head injury (including neurosurgery) or have you ever been taken to hospital following an injury to the head?	☐Yes ☐No
Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?	☐Yes ☐No
Do you have any implanted devices such as cardiac pacemakers, aneurysm clips, cochlear implants, medical pumps, deep brain stimulators, or intracardiac lines?	☐Yes ☐No
Do you suffer from frequent or severe headaches or have you ever experienced a migraine?	☐Yes ☐No
Have you ever had any other brain-related condition?	☐Yes ☐No
Have you ever had any illness that caused brain injury?	☐Yes ☐No
Are you taking any psychiatric or neuroactive medications (e.g. antidepressants), or do you have a history of drug abuse?	☐Yes ☐No
Are you pregnant?	☐Yes ☐No
Do you, or does anyone in your family, have epilepsy?	☐Yes ☐No
Do you hold a heavy goods vehicle driving license, pilot's license, or bus license?	☐Yes ☐No

I have read and understood the questions above and have answered them correctly.

SIGNED…… DATE……

In the presence of …….. (Name) …….. (Signature)

DEFINITIONS OF TECHNICAL TERMS

PACEMAKER: An electronic device that is surgically placed in the patient's body and connected to the heart to regulate the heartbeat.

COCHLEAR IMPLANT: An electronic medical device that bypasses damaged structures in the inner ear and directly stimulates the auditory nerve, allowing some deaf individuals to learn to hear and interpret sounds and speech.

ANEURYSM CLIP: A surgically implanted metal clip used to cut off blood flow through the neck of an aneurysm. An aneurysm is a deformity of a blood vessel in the body, which can swell and burst causing a haemorrhage.

SHUNT: A surgically implanted connector, which allows passage of fluid between two parts of the body. A common use of a shunt is to allow fluid to drain away from the brain, thus reducing pressure in the brain. May also describe a tube which allows blood to be moved from one part of the body to another.

STENT: A surgical implanted device that is inserted into a blood vessel to provide support, keep the vessel open and promote unblocked and enhanced blood flow. Sometimes used in other fluid carrying vessels in the body such as bile ducts etc.

TMS Pre-Session Screening

To minimise the risk of TMS causing an adverse effect, it is important that you answer the following questions accurately before we begin the session.

---

1) In the last 12 hours, have you consumed more than 3 units of alcohol or any recreational drugs?

☐ Yes ☐ No

---

2) Did you get a good night's sleep last night, and do you feel alert?

☐ Yes ☐ No

---

3) In the last two hours, have you consumed more than two cups of coffee or any other caffeinated drinks?

☐ Yes ☐ No

Date…….

Name…….

Signature…….

Transcranial Magnetic Stimulation (TMS)

Monitoring Questionnaire

As part of our research programme, we routinely monitor the health of participants following TMS. We would be grateful if you could answer the questions listed below. Completing this form is entirely voluntary. The information you provide will be treated as confidential and will be held in secure conditions. Group results of this survey may be published, but no information will be disclosed that can identify any individual person.

If you are unsure how to answer any of the questions, please ask the researcher who gave you this form.

Name:
Current Date:
Date of Birth:
Handedness:

Please tell us if you experienced any of the following symptoms in the 24 hours following your most recent TMS session. If the answer is YES to any of these questions, we would be grateful for additional details

Seizure

☐Yes ☐No **Details:**

Fainting or Collapse

☐Yes ☐No **Details:**

Dizziness

☐Yes ☐No **Details:**

Nausea or vomiting

☐Yes ☐No **Details:**

Headache

☐Yes ☐No **Details:**

Muscular aches

☐Yes ☐No **Details:**

Muscle spasm or twitch

☐ Yes ☐ No **Details:**

Insomnia

☐ Yes ☐ No **Details:**

Sensory Problems

☐ Yes ☐ No **Details:**

Difficulties speaking or understanding speech

☐ Yes ☐ No **Details:**

Lack of coordination

☐ Yes ☐ No **Details:**

Slowness or impairment of thought

☐ Yes ☐ No **Details:**

Other (please specify)

☐ Yes ☐ No **Details:**

Any other comments

Do not write below this line (for staff use only)

Details of protocol undertaken TODAY: to be completed by researcher following session

Researcher	Experiment	Sham/Active/Both	TMS Frequency	TMS Intensity	No. Pulses