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How can clinicians detect and treat autism early? Methodological trends of technology use in research

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Abstract

We reviewed original research papers that used quantifiable technology to detect early autism spectrum disorder (ASD) and identified 376 studies from 34 countries from 1965-2013. Publications have increased significantly since 2000, with most coming from the USA. Electroencephalogram, magnetic resonance imaging and eye-tracking were the most frequently used technologies.

Conclusion—The use of quantifiable technology to detect early ASD has increased in recent decades, but has had limited impact on early detection and treatment. Further scientific developments are anticipated and we hope that they will increasingly be used in clinical practice for early ASD screening, diagnosis and intervention.

Keywords

early autism spectrum disorder; electroencephalogram; eye-tracking technology; magnetic resonance imaging; review

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Introduction

The concept of autism spectrum disorder (ASD) has changed since the reports by Leo Kanner and Hans Asperger in the 1940s. There have been many shifts in research priorities and paradigms (1) and an exponential growth in research since the mid-1990s (2). Almost three times as many studies on autism were published between 2000 and 2012 (n=16,741), as between 1940 and 1999 (n=6,054) (2). Between 2005 and 2009 alone, the number of publications on autism rose five-fold, compared to 1985-1989. Some of the factors accounting for the disproportionately high rise in ASD research activity include an increase in diagnoses, the involvement of scientists from a wider range of disciplines and increased funding (3). The vast majority of the ASD research that has been conducted so far has examined individuals from mid childhood onwards. This is surprising, as the major diagnostic systems - the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders and the tenth edition of the International Classification of Diseases – state that an early onset of symptoms is essential for core autism and other forms of ASD. A simple explanation for this is that in the past most children with ASD were diagnosed in later childhood, although it is still the case that more subtle variants tend to be recognised when patients are older (4). Fortunately, there has been an increase in the research and clinical attention paid to ASD in infancy and toddlerhood, owing to increased awareness that identifying ASD early can lead to early intervention, which can improve outcomes (5). As a result, ASD research priorities now include the development of screening instruments to prospectively identify ASD in clinical and population-based settings (6), retrospective analyses of home videos to improve the knowledge of early signs of ASD (7) and early intervention studies to improve ASD outcomes (8–10). However, such studies on their own are probably not an effective way of monitoring and deciphering the developmental trajectories of the complex neurobiological systems and psychological processes that precede ASD. These are crucial if we are to further improve risk assessments, early diagnoses and the timely and individual interventions that are needed. Prospective assessments of infants at risk of ASD aim to characterise these developmental and potentially pathogenic pathways, particularly for those who face a high family risk as they have one or more older siblings with ASD (11).

Studies of research into early ASD involve a multitude of methods to examine development in the first months and years of life, as well as responses to interventions. These methods might provide information that help us to understand the difference between typical and atypical developmental trajectories, assist early ASD diagnoses and provide new leads and targets for early treatment. These methods can be classified into two groups. One group comprises classical informant and clinician-based behavioural methods, like questionnaires, observation scales, interviews and developmental tests. These can be summarised as observational, subjective and sometimes qualitative. The other group consists of methods that are either technology based and, or, measure basic cognitive or neurological processes and structures. These can be summarised as direct, objective and mostly quantitative. The second group of methods included eye-tracking, electroencephalography (EEG), event-related potentials (ERPs), magnetoencephalography (MEG), functional and structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), positron emission

tomography (PET), single-photon emission computed tomography (SPECT), near infrared spectroscopy (NIRS) and transcranial magnetic stimulation (TMS). They also included different forms of video-technology, such as video modelling for teaching purposes, retrospective video analysis for diagnostic purposes and preferential looking experiments. The more objective technology-based techniques of research into early ASD have greater potential to reveal previously unknown subtle atypicalities in the developmental processes leading to ASD, rather than classical, subjective measures on their own. Even though methods are still, to a large extent, based on preclinical science, technology-based approaches to detecting ASD have potential for paediatric and child and adolescent psychiatric clinical practice. This is because they seek to identify biological markers of ASD for earlier diagnosis and biologically-defined treatment goals. Technology-based techniques have been increasingly applied in prospective longitudinal studies of infants at high risk for ASD and have provided insights into the complexity of how ASD unfolds and the early underlying mechanisms (12).

This review formed part of the COST Action Enhancing the Scientific Study of Early Autism (ESSEA) project, funded by The European Science Foundation between 2010-2014, which aimed to develop European capacity in early autism science through networking, laboratory exchanges, bi-annual meetings, summer schools for early stage researchers and conferences. The project involved 50 scientists from 20 European countries and one of the four subgroups was tasked with studying the use of new technology (www.cost-eassea.com). The review had three specific aims. First, we wanted to review published studies on technology-based research into early ASD, based on the country of origin, publication year, type of technique and specific methods applied, sample characteristics such as sample size and gender distribution, whether the risk status was diagnosed or at risk, controlled and uncontrolled studies, cross-sectional and longitudinal studies, funding sources, journal and journal impact factor. Our second aim was to to examine changes in research priorities and characteristics over time. The third aim was to analyse differences in publication activity between the transnational regions of North America, Europe and the rest of the world. Therefore, this work provides a comprehensive descriptive overview of international structural and quantitative changes in technology use in research into early ASD and its funding. The findings look at the development of this line of ASD research in the past, give an indication of the direction the field may be moving in and the clinical significance of developments to date.

Methods

Search strategy

We used a PRISMA approach to systematically search for empirical studies that used technology to study individuals who were up to five years of age and who had ASD or faced an increased risk of developing ASD. Studies were identified by searching electronic databases that included MEDLINE, PubMed, PsycINFO, ERIC and Cochrane using medical subject headings (MeSH) and relevant words. The detailed search criteria is outlined in Appendix 1.

We carried out two systemic searches in September 2013 and January 2014 to ensure consistency and to include all further relevant articles published between 1 September 2013 and 31 December 2013. Both of these searches were carried out by an information specialist at the University Library, Karolinska Institutet, Stockholm, Sweden. After the second search, the third author (UJ) created an Endnote database using Endnote Version X6 (Thompson Reuters, Philadelphia, USA). This database included pdf files of the articles. In addition, a semi-automatic duplicate extraction was carried out before starting the detailed analyses. This process resulted in a total of 3,028 papers. The Endnote database was then manually checked for duplicates by two authors (KDB, DZ) and another 251 duplicates were deleted, resulting in a total of 2,777 papers for analysis.

Data extraction

This study focused on original papers published in peer-reviewed journals that studied infants or children with ASD, or at increased risk of ASD, who were younger than five years of age at the start of the study. Studies were included if participants were diagnosed with ASD, including Asperger's syndrome, pervasive developmental disorder - not otherwise specified (PDD-NOS), autistic disorder and atypical autism. We excluded studies on participants with autistic-like behaviours or autistic features, but without a mentioned diagnosis of ASD, and studies on participants with an additional diagnosis of conditions like fragile X syndrome, tuberous sclerosis or epilepsy. Manuscript formats other than original papers, and those that did not use one of the specified technologies, were also excluded. Two reviewers independently screened the 2,777 titles, abstracts or manuscripts. We obtained the full texts of all papers that were judged to meet the eligibility criteria by at least one reviewer and two authors independently assessed them to see if they should be included. If a paper was excluded after the full text was reviewed, the reason for excluding it was recorded. Any disagreements at this stage were resolved by discussions and if no agreement could be reached then a third author decided. A second author checked the data extraction. Reference lists were screened for other relevant studies and we randomly selected 10% of the references in the Endnote database, just before it was finalised, and they were analysed by two independent raters (KDB, DZ). A total of 301 papers were double coded to establish interrater reliability and this revealed that the Cohen's kappa for reference inclusion was $\kappa = 0.85$ and that the kappa for the detailed evaluation, which comprised assigning characteristics 1-11 (see below), was $\kappa = 0.95$. Finally, 2,401 of the 2,777 papers were excluded and the remaining 376 papers that we wanted to analyse were exported to an Access database (Microsoft Corporation, Washington, USA) for detailed documentation. Data was extracted from each of the studies that were included and inserted into an extraction sheet by one author. After we assigned an identification number for each publication we systematically extracted the following characteristics: 1) authors, country of origin and transnational region, 2) year of publication, 3) journal and its impact factor, 4) title of paper, 5) technologies used, 6) number of participants, 7) gender distribution, 8) diagnosis or risk status – ASD, autistic disorder, PDD-NOS, Asperger's syndrome, atypical autism or at risk of ASD, 9) if a control group was included, 10) cross-sectional versus longitudinal studies and 11) funding sources. If the country of an original study was not explicitly stated in item 1) we assumed that the trial was conducted in the country covered by the ethical review board or the university or institution of the corresponding author. The

transnational regions were Europe, North America or other. With regard to the impact factor in item 3), this was based on the year that the paper was published and retrieved from the Journal Citation Reports produced by Thomson Reuters in 2012.

We were unable to obtain complete data for all the study characteristics for 30 papers, as they were not reported in the publication and repeated attempts to collect them retrospectively from the authors were not successful. Despite this, we still included these papers in our review.

Results

We identified 376 articles that used specific technology to examine the early stages of ASD and 265 of these included at least one control group, 256 had a cross-sectional design and 120 had a longitudinal design. A total of 17,227 individuals participated in these studies and of these 18.8% were girls, 74.0% were boys and in 7.2% of cases the gender information was missing. The gender ratio was reported in 344 studies. We noted that 38 studies with 1,714 participants examined individuals with a high risk of ASD and, of these, 47% were boys, 41% were girls and 12% had missing gender information.

The papers we selected came from 34 countries: 198 papers from the USA, 34 from Italy, 27 from Japan, 18 from the UK, 17 from France, 15 from Sweden, nine each from Canada and Australia, five from Israel, four from the Czech Republic, three each from China, Egypt, Russia, Switzerland and Turkey, two each from Brazil, Greece, Hong Kong, India, Korea and the Netherlands and one each from Belgium, Cuba, Denmark, Germany, Ireland, the Former Yugoslav Republic of Macedonia, Norway, Romania, Serbia, Singapore, South Africa, Spain and Tunisia. Four papers involved collaboration between two countries, namely the USA and Israel, the UK and Canada, Sweden and Russia and Sweden and the Netherlands. Based on the origins of the studied populations one paper was assigned to the USA, one to the UK and two to Sweden. This meant that 110 papers originated in Europe, 207 papers came from North America and 59 papers were from other parts of the world.

This review included articles published between 1965 and 2013, but we noticed an exponential growth in the number of publications, particularly in the last two decades, with about two-thirds (n=250) of the studies being published in the last 10 years. The increase in the number of publications was more pronounced for research into early ASD conducted in North America than in other geographical regions (Figure 1). Given that most studies were published in the past decade, a more detailed look at the number of publications in this period revealed that MRI, eye-tracking and EEG studies had increased the most, while the use of video technology had decreased. The use of DTI and ERP was low but relatively stable, while SPECT, PET, MEG and NIRS were too rarely used to draw any firm conclusions about the changes.

The most frequently used technologies were EEG and ERP, in 129 of the reviewed papers, functional and structural MRIs in 114, eye-tracking in 47, retrospective video analysis in 44 and video modelling in 29. None of the reviewed papers used TMS. The frequencies of all these methods can be found in Table 1. The first paper that used EEG to study early ASD

was published in 1965, while the first NIRS study appeared in 2013. The years when other methods were used to research early ASD were as follows: ERP (1980), eye-tracking (1985), functional and structural MRI (1987), PET (1987), video and retrospective analysis (1990), SPECT (1993), video analysis and referential looking (1994), video modelling (1998), MEG (1999) and DTI and MRI (2007). The methods differed with regard to how often they were used in different geographical regions (Figure 2). Some methods, such as DTI, were mostly used in North America, while the use of other methods like EEG were more widely distributed. SPECT was predominantly used in geographical regions outside Europe and North America.

Global research into early ASD was funded by 530 approved grants from 152 different funding sources. More than half of all the grants were from eight agencies: 183 grants from the National Institutes of Health, 29 from Autism Speaks, 16 from the Simons Foundation, 15 from the UK Medical Research Council, 12 from Cure Autism Now, 12 from the European Union, 10 from the National Alliance for Autism Research and 10 from the British Autism Study of Infant Siblings funding consortium. In Europe, 65% of the published papers reported the funding sources, in North America it was 74% and in the other countries it was 29%. European researchers obtained their funding from 60 different grant-making agencies and foundations, with 55 of those being European and five based in the USA. In North America, research funding came from 87 different agencies, with 75 based in the USA, five in Canada, five in Europe and two in Japan. Researchers from other countries received funding from 17 agencies and, of these, three were from the USA and 14 were from national agencies in their own country.

The 376 articles we selected were published in 147 different journals. The 10 journals that published the highest number of articles were: the *Journal of Autism and Developmental Disorders* with 46 papers, the *Journal of Child Neurology* with 19, *Brain and Development* with 18, the *Archives of General Psychiatry* with 15, *Biological Psychiatry* with 14, *Developmental Science* with eight, the *Journal of the American Academy of Child and Adolescent Psychiatry* with eight, *PLOS ONE* with eight, *Research in Autism Spectrum Disorders* with eight and *Developmental Medicine and Child Neurology* with seven. Other leading journals that had published research into early autism were: the *American Journal of Psychiatry* with five papers, *PNAS* with four, *Nature* with two papers and *Neuron* and *JAMA* with one each. There were 24 articles (6.4%) published in journals with an impact factor of more than 10 in the respective year between 1987 and 2013, 22 from the US and two from France. The median impact factors for the journals that published the papers on early autism research using technologies was 3.47 for papers from North America, 2.01 for papers from Europe and 1.67 for other countries. The type of methodology used in the studies seemed to be associated with the impact factor level of the journal it was published in. For example, studies that used DTI, preferential looking and eye-tracking were published in the journals with the highest median impact factors (Table 1).

Discussion

This systematic review examined international trends in research into early ASD since 1965, and their potential impact on clinical practice, by focusing on publication activity and

funding using various technologies and objective measures. In line with ASD research in general (2), research output has increased substantially in this field, particularly in the last decade. Papers on this subject are currently published in a broad range of journals with low to high impact factors, covering specific ASD areas, child and adolescent psychiatry, paediatrics, neurology, general psychiatry and multidisciplinary subject areas.

Although the number of published articles increased exponentially, even in Europe and other parts of the world, the majority of the research originated in North America, especially the USA. Moreover, a large number of the studies published in high impact journals were conducted in North America and the same was true for funding sources. Even though a multitude of governmental and private organisations around the world support ASD research based on novel methods, the National Institutes of Health in the USA sponsored nearly 50% of all the studies into early ASD covered by this review, compared to just 3% sponsored by the European Union.

With regard to methodological trends, this review showed that EEG had been used in research into early ASD for a long time and had generated a large number of publications. Researchers who are starting their career might find it useful to know that more and more research has been carried out into functional MRI as well as eye-tracking and ERP in the last 10 years. For example, there is substantial interest in eye-tracking technology, which is optimal when studying infants and young children and can provide information on various aspects of development (13). It is also, perhaps, the method that is currently viewed as having the highest direct clinical potential for early paediatric screening of ASD, possibly because it is not intrusive. DTI or MRI and NIRS have only recently been applied in a smaller number of studies, but these technologies have achieved good visibility in high impact journals. The focus on technologies in early ASD development puts new demands on autism researchers, ranging from technical expertise to practical know-how (14). These can partly be solved by cross-disciplinary collaboration, for example between child psychiatrists and infancy researchers, but they will also need to be reflected in training programmes for new scientists entering the ASD field.

An inherent limitation of most reviews, including the current one, is that there is a certain risk of findings being partly obsolete by the time they are published, owing to the large and increasing number of papers being submitted to, and published by, journals. However, this review is probably still sufficiently representative of the current situation and provides an accurate summary of the use of technology in research into early ASD. Having said that, the results should not be confused with other areas of ASD research, where the publication activity and development, international representation, scientific impact and funding situation might be different. For example, we did not look at the development of publication activity in research into early ASD with regard to what we earlier described as classical methods, such as questionnaires, observation scales, interviews and developmental tests. Nevertheless, it is likely that publication activity has also increased in other areas of ASD research. This can be concluded from the fact that ASD research in general is growing and that most technology-based studies also include classical elements.

Furthermore, we did not analyse whether the average age of the participants included in technology-based ASD studies changed over time or if certain technologies were more frequently used in particular age groups than others. Nevertheless, it is likely that the average age of the participants has dropped significantly in the last decade, as the first assessment for ASD often takes place six months after birth, thanks to the publication of studies into the high risks that infants face if they have siblings with ADS. In any case, analysing the frequency that technology is used in different age groups would not have been very informative owing to the rather small number of studies in specific categories. This review was descriptive and only focused on technology use in the early detection of ASD. Therefore, it cannot answer why and how the observed changes appeared and whether they were specific to the early development of ASD, for other fields of ASD or other mental conditions or for early development research in general.

In addition, we did not evaluate the quality of all the included studies using common schemes such as the Consolidated Standards of Reporting Trials. Thus, this study essentially reported quantitative rather than qualitative changes. On balance, all of the studies were original and had gone through the peer-review process, which is likely to have ensured they met basic scientific standards. In addition, and based on the experience of the authors of this study, demands for high-quality science in this field have increased rather than decreased.

Our mapping findings indicate that research into early ASD using objective technologies has rapidly evolved around the world in the last few decades. This is a prerequisite, but not a confirmation, of an ongoing paradigm shift going on in the ASD field, whereby objective technology-based measures are slowly, but steadily, replacing subjective classical measures in clinical practice. Early detection of, and intervention in, ASD cases has indeed improved in clinical practice. This review was unable to determine whether research into early ASD had fuelled clinical improvements or vice-versa. Technology-based research studies have certainly thrown a spotlight on early autism and they encourage clinical scientists and practitioners to develop new ways of working with young children and families. It is clear that technology-based research in ASD is accelerating. However, to date, no one technology or combination of technologies have improved the reliability or validity of diagnostic procedures or the efficacy or effectiveness of interventional practices in ASD. Such developments are still driven by classical behaviour-based tools, such as the Autism Diagnostic Observation Schedule - 2 (15), which provides a module to assess ASD in toddlerhood. There still seems seems to be some kind of parallel between the quality and output of technology to detect early ASD technology research and the development of clinical services. Furthermore, high-quality, technology-based research into early ASD is more likely to drive awareness and policy changes, as it appears more scientific and convincing to the public and is therefore more likely to receive media coverage.

Scientific breakthroughs of technology-based early ASD detection might be in reach, thanks to the more recent introduction of methods such as DTI or further advances in methods such as molecular imaging - PET and MRS - which are potentially more sensitive to developmental alterations in ASD than older methods. These methods may also translate more easily into other areas of basic and applied science, such as animal modelling and drug development (16). In addition, some technologies, such as non-invasive eye-tracking, might

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be easier to apply to the whole ASD population, not just to those participants who are able to participate in methods like psychological testing. The latter could potentially lead to more objectively measurable, quantifiable and generalisable phenotypes. These could, in turn, be translated to family genetic research and inform both typical and atypical neurodevelopment. Finally, having knowledge about both the typical and atypical development of functions could enable us to define new treatment targets and use neuroplasticity to treat and train patients towards neurotypicality (17, 18). It is important to keep in mind that this technological advancement has to be accompanied by increased harmonisation of the protocols between laboratories, data sharing, longitudinal outcomes, integrated multilevel assessments and larger sample sizes that enable the analyses of more homogenous ASD subsamples. Such joint efforts are ongoing in research into early ASD in large consortia research projects, such as the Infant Brain Imaging Study (www.ibisnetwork.org), the Baby Sib Research Consortium (www.autismspeaks.org/site-wide/bsrc) and the European Babysibs Autism Research Network (www.eurosibs.eu). The anticipated findings of these studies, and the findings of this review, lead us to expect even more intense research activity into the detection and treatment of early ASD. We also look forward to the introduction of future technologies that will result in major scientific developments that will possibly, and gradually, start to concretely influence diagnostic and intervention practices in paediatrics, child psychiatry and neighbouring disciplines.

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Appendix 1: The detailed search criteria employed by this study.

This Appendix contains the search combined index terms (exploded) with specific words searched for in abstracts and titles. In order to retrieve articles not yet indexed in MEDLINE, a complementary search of just abstracts and titles was run in PubMed. Methods included in the search were: eye-tracking, electroencephalography, event-related potentials, magnetoencephalography, functional and structural magnetic resonance imaging, diffusion tensor imaging, positron emission tomography, single-photon emission computed tomography, near infrared spectroscopy and transcranial magnetic stimulation. We also included different forms of video-technology, such as video modelling for teaching purposes, retrospective video analysis for diagnostic purposes and preferential looking experiments.

The full search strategy in MEDLINE was as follows:

1) exp Child Development Disorders, Pervasive /

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2) (autis* or asperger* or pervasive or PDD or PDD-NOS or pervasive develop*).abstract, title.

3) 1 or 2

4) exp Electroencephalography (EEG) /

5) exp Magnetic Resonance Imaging (MRI) /

6) exp Positron-Emission Tomography (PET)/

7) exp Diffusion Tensor Imaging (DTI)/

8) exp Spectroscopy, Near-Infrared (NIRS) /

9) exp Event-Related Potentials (ERP), P300 /

10) exp Transcranial Magnetic Stimulation (TMS) /

11) exp Magnetoencephalography (MEG)/

12) exp Siblings /

13) EEG or Eye-tracking or functional MRI or structural MRI or MRI or SPECT or Single-photon emission computed tomography or PET or DTI or NIRS or Near-infrared spectroscopy or functional NIRS or ERP or Event-related potential or TMS or MEG or video* or high risk or at risk or sibling*).abstract,title.

14) Electroencephalography or Magnetic Resonance Imaging or Positron-Emission Tomography or Diffusion Tensor Imaging or Spectroscopy, Near-Infrared or Event-Related Potentials, P300 or Transcranial Magnetic Stimulation or Magnetoencephalography).abstract,title.

15) exp Eye Movements /

16) Video Recording /

17) exp Infant /

18) exp Child, Preschool /

19) (infant* or baby or babies or toddler or girl* or boy* or pre*school*).abstract,title.

20) 17 or 18 or 19 (21) 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

22) 3 and 20 and 21

23) remove duplicates from 22

24) limit 23 to English language.

List of Abbreviations Used

ASD	autism spectrum disorder
DTI	diffusion tensor imaging

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EEG	electroencephalography
ERPs	event-related potentials
MEG	magnetoencephalography
MRI	magnetic resonance imaging
NIRS	near infrared spectroscopy
PDD-NOS	pervasive developmental disorder-not otherwise specified
PET	positron emission tomography
SPECT	single-photon emission computed tomography
TMS	transcranial magnetic stimulation

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Key Notes

- The use of quantifiable technology to detect early autism spectrum disorder (ASD) has increased in recent decades, but has had limited impact on early detection and treatment.
- Our review identified 376 published studies from 34 countries between 1965-2013 and showed that research publications have increased significantly since 2000, mostly from the USA.
- The most frequently used technologies to detect early ASD were electroencephalogram, magnetic resonance imaging and eye-tracking.

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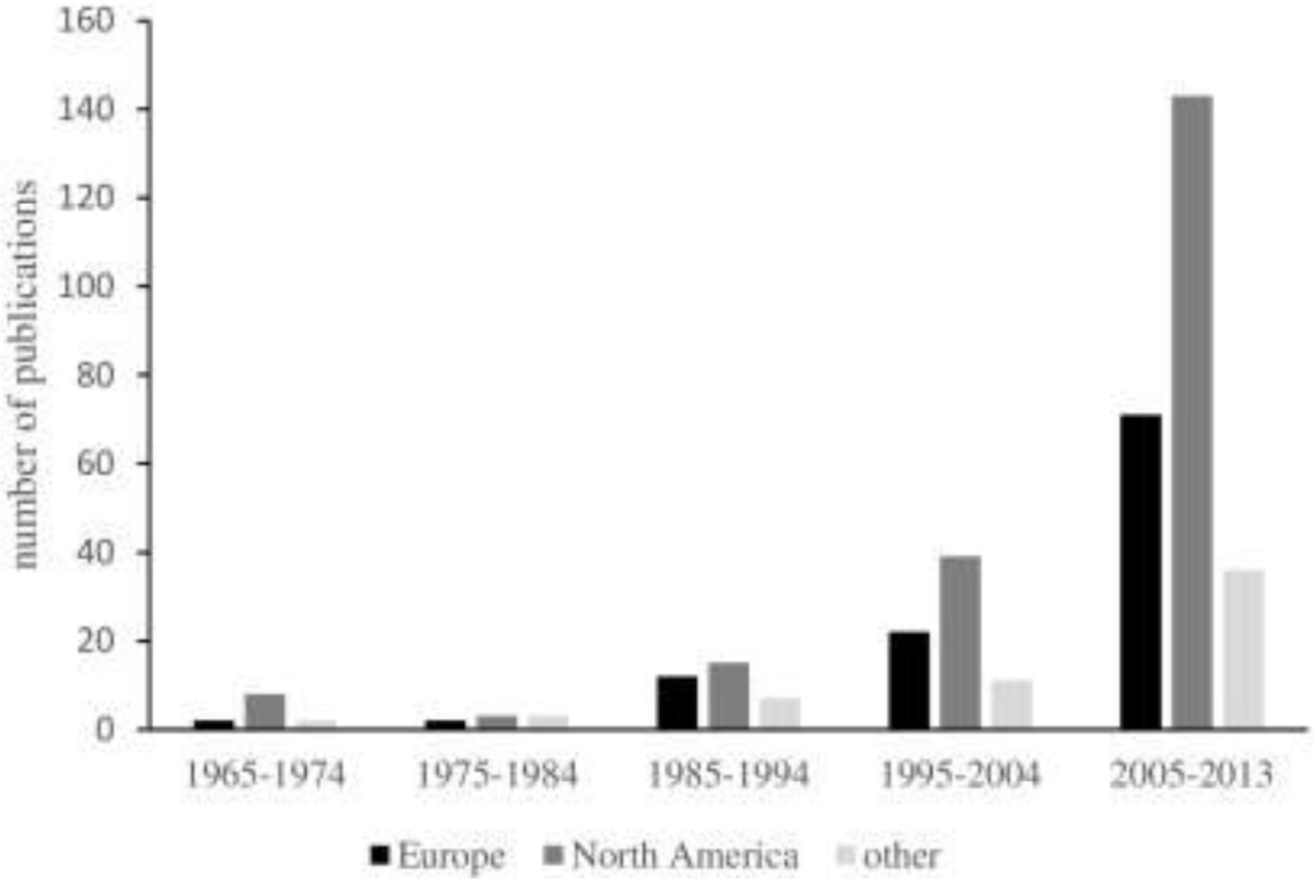

Figure 1.
Number of publications per geographical region in total and split by decades.

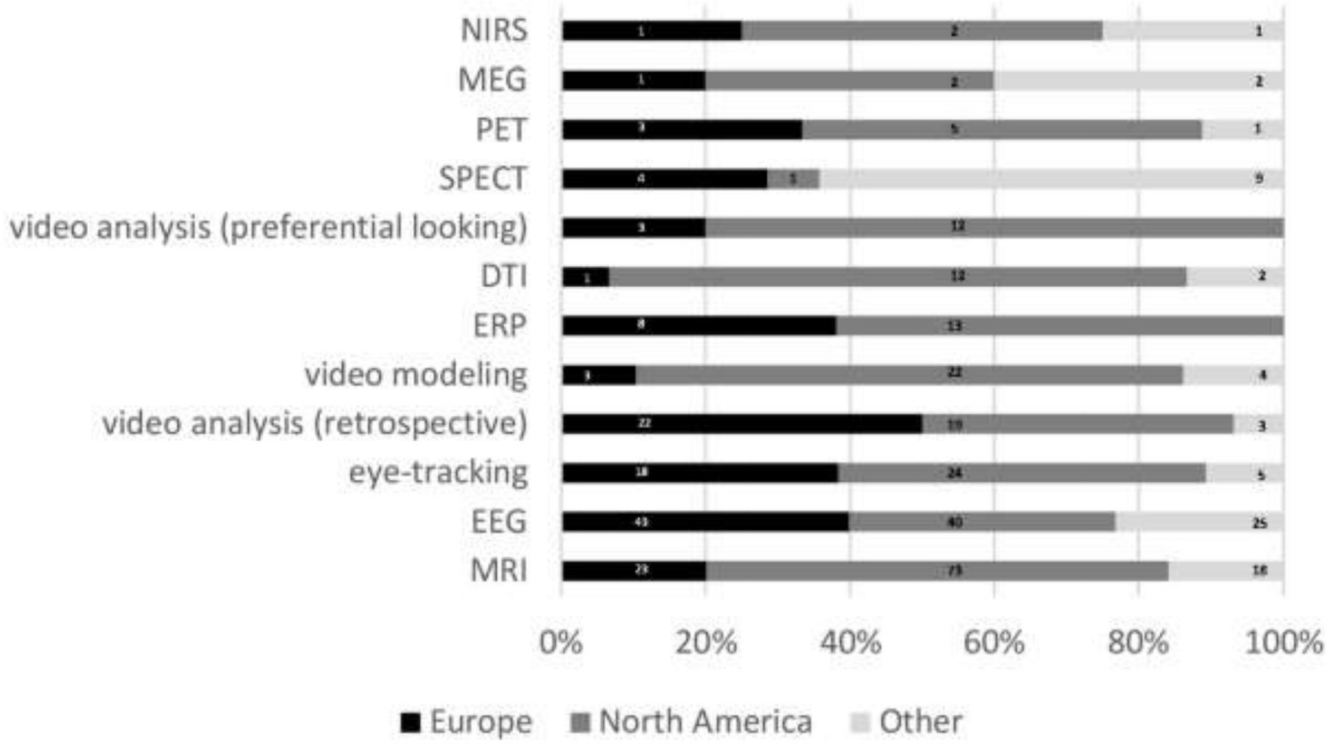

Figure 2.
Research utilising each of the reviewed methods per geographical region, in percentages with the actual numbers of the studies in the bars.

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Table 1

Number of studies that used one of the reviewed methods in each period and in total, together with the median impact factor for each method.

	1965 - 1974	1975 - 1984	1985 - 1994	1995 - 2004	2005 - 2013	Total	IF
MRI	0	0	15	29	70	114	3.24
EEG	11	7	11	22	57	108	1.98
Eye-tracking	0	0	1	1	45	47	3.72
Video analysis (retrospective)	0	0	6	12	26	44	2.58
Video modelling	0	0	0	5	24	29	1.34
ERP	0	1	0	3	17	21	3.36
DTI	0	0	0	0	15	15	4.33
Video analysis (preferential looking)	0	0	1	0	14	15	4.09
SPECT	0	0	1	8	5	14	1.09
PET	0	0	2	4	3	9	2.09
MEG	0	0	0	1	4	5	3.23
NIRS	0	0	0	0	4	4	2.91

Abbreviations: MRI, magnetic resonance imaging; EEG, electroencephalography; ERPs, event-related potentials; DTI, diffusion tensor imaging; SPECT, single-photon emission computed tomography; PET, positron emission tomography; MEG, magnetoencephalography; NIRS, near infrared spectroscopy.